# MODERN TRENDS

IN

# GASTRO-ENTEROLOGY

(SECOND SERIES)

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IN

# GASTRO-ENTEROLOGY

(SECOND SERIES)

*Edited by*

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M D F R C P

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# FOREWORD

WE ARE living in an interesting phase of medical reorientation The historic dis tinction between physicians and surgeons dating from the Papal Bull of A D 1215 is being replaced by specialization of a different sort based on regions or groups of diseases Of these the most recent is gastro enterology—the study of diseases of the alimentary tract and its related glands

This second volume in the series illustrates well the immense value of such con centration of interest whereby the attention of men of diverse disciplines is focused on a single field for here are physicians and surgeons anatomists and radiologists physiologists pathologists and biochemists all making their contributions to the common pool of knowledge

This volume may be regarded as complementary to the first in the series It is in no sense a systematic treatise but rather concentrates attention on particular diseases new methods of investigation and related features of interest

In selecting his team of contributors Dr Avery Jones has shown fine judgment and discrimination He has ranged over most of the western world and without exception his collaborators speak with the authority which comes from mastership of their special fields There can be no doubt that the book will be assured of a good welcome

C F W ILLINGWORTH

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# INTRODUCTION TO THE SECOND SERIES

THE ADVANCE of gastro enterology has proceeded more slowly than for example the advance of cardiology mainly because there have been fewer new techniques to use as the tools of research However good progress has been made and the momentum is increasing particularly with the development of isotope studies improved methods of determining gastric secretion and the introduction of cine photography and new devices for recording pressure changes The one striking advance therapeutically has been the introduction of gluten free diet for the control of coeliac disease in children and for a proportion of adult patients with steatorrhoea The alimentary tract has shared with other systems the benefits and disadvantages from antibiotics and the corticosteroids and these subjects are reviewed in Chapters 2 and 3 It is interesting that since the First Series was published five years ago progress has continued along simple clinico pathological lines and that new syndromes and physical signs have continued to be described The most important of these have been first the clinical syndrome du- to car cinoid tumours of the alimentary tract and their associated metastases described in Chapter 6 by Waldenström Pernow and Morson and secondly the syndrome of portal systemic encephalopathy in its chronic form with which is usually associated cirrhosis hepatis with a large collateral circulation A new and not uncommon cause of haematemesis actually described some years ago but again brought into prominence is the Mallory Weiss syndrome (page 205) which is due to longitudinal lacerations at the cardio oesophageal junction due in turn to the strain of vomiting It is essentially a lesser degree of the injury which has been well recognized as the cause of rupture of the oesophagus Barrett (Chapter 9) has contributed appreciably to our knowledge of the anatomy of the lower oeso phagus and cardia and has given recognition to the gastric mucosa lining the lower part of an otherwise normal looking gullet Large chronic ulcers (Barrett s ulcers) occur in this type of mucosa and not in the squamous epithelium of the true oesophagus Studies by Marchand (1955) have contributed to a clearer under standing of the forces concerned with oesophageal reflux and the genesis of hiatus hernia At the present time much work is being done which combines pressure recordings and cinephotography and which will further clarify deviations from normality of gastro intestinal motility and sphincter control It will undoubtedly be well represented in the Third Series of *Modern Trends in Gastro enterology*

Good progress has been made in relation to small intestine dysfunction The importance of the blind loop syndrome in the production of steatorrhoea anaemia and peripheral neuritis has been clarified and our present knowledge brought together by Badenoch in Chapter 15 The metabolic effects of intestinal resection have been the subject of special study by Jackson (Chapter 16) Important work is still in progress concerned with factors controlling absorption of folic acid and vitamin $B_{12}$ The introduction of the gluten free diet has been found to benefit an appreciable proportion of patients with idiopathic steatorrhoea in adults as well as coeliac disease in children Important studies by Weijers et al (1957) have recently been published and have identified gliadin as the particular fraction of gluten protein responsible for the metabolic disturbance The Peutz Jeghers syndrome of

M h d P (1955) *B i J S g* 42 N 175 504 P w B (1951) *A Ph of S and* 24 97 W jers
H A V d K m J H d D k W I C (1957) *Ad nc P d i ic* Ch g Th Y Book P bl h rs

intestinal polyposis and mucosal pigmentation has become better known and has been reviewed by Dormandy (Chapter 7) The time is opportune for bringing together our knowledge of collagen diseases affecting the bowel and this has been done by Bourne (Chapter 4) Whipple s disease or intestinal lipodystrophy has assumed a new pathology This disease causes a sprue like syndrome with rheumatic and serous membrane manifestations and produces a characteristic histological lesion with the presence of macrophages in the lymph nodes and mucosa of the small intestine *These stain with the PAS (periodic acid schiff) and have now been shown* to be due to the presence of a glyco protein It is thought the polyserositis represents a state of hypersensitivity to the muco protein substance (Puite and Tesluk 1955)

*Ulcerative colitis unfortunately still remains the outstanding unsolved problem* of the large intestine but there has been a steady increase in our knowledge of its natural history which has been studied in the United States of America by Bockus and his colleagues (Chapter 19) Not all will agree with his conclusions concerning the disappointing value of corticosteroid therapy and many will share Witts appraisal of its value (Chapter 2)

In relation to liver diseases much has been learnt of the factors concerned with hepatic coma and this is fully discussed by Sherlock (Chapter 23) who has done much of the work in this field The mortality from hepatic coma has been reduced by a new therapeutic approach based on a clear understanding of its genesis and an important clinical advance has been the recognition of portal systemic encephalopathy associated with a large collateral circulation and responding often dramatically to a reduction of protein intake It is interesting to find a new physical sign in cirrhosis hepatis described by Terry (1954) who noted the special appearance of the nails in these patients The most valuable diagnostic advance has been the introduction of the intravenous cholangiogram and our present knowledge of this technique has been set out by Cummack (Chapter 21)

The observations of Aird and his colleagues on the association of duodenal ulcer with blood Group O is providing a new research approach to the problem The role and mechanism of hyperacidity and anacidity has received much attention since the introduction of the special test by Kay (1953) for the maximum secretory activity of the stomach (page 180) This has firmly established the relationship of hyperacidity and achlorhydria to parietal cell mass Hunt has continued to illuminate the mechanism of gastric motor and secretory function with special reference to peptic ulcer using his special test meal technique (Chapter 10) There have been special studies on giant ulcers and post bulbar duodenal ulcers and these and other diagnostic problems are discussed by Pygott (Chapter 8) With medical treatment there is less emphasis now on strict dietary regimes Doll and Pygott have concluded that of many remedies tested only bed rest and abstention from smoking can be shown to accelerate the healing of gastric ulcers The present surgical position is reviewed by Tanner (Chapter 12)

There has been a real advance in the cytological diagnosis of cancer of the alimentary tract by examination of irrigating fluids for malignant cells The considerable degree of accuracy achieved by Raskin Kirsner and Palmer is described in Chapter 5 Section III Unfortunately the technique is rather laborious and needs suitable experience but it is clearly a method which must be available for specialized

A d I Be t ll H H M h ga J A a d F ase R be t J A (1954) *B t m d J* 2 315 K y A W (1953) *B t m d J* 2 77 Pu e R H d T l k H (1955) *Am J M d* 19 383 Te y R (1954) *Lan t* 1 757

units Oesophageal gastric duodenal pancreatic and colonic neoplasm may all be demonstrated by this technique

There has been a steady accumulation of careful studies in relation to pre malignancy (Chapter 5) and in the assessment of surgical treatment as illustrated in relation to the large intestine by Naunton Morgan (Chapter 20) The importance of environmental carcinogens has been illustrated in the work on smoking and cancer of the lung and this has raised the serious possibility of other carcinogens which play a role in the development of alimentary tract cancer This possibility is increased by the demonstration of big geographical variations in cancer of the stomach which are discussed by Doll in Chapter 5 Section I Similar variations are known to occur in carcinoma of the large bowel

Recent years have seen a flood of publications on psychosomatic medicine but the tide is clearly receding No one concerned with gastro-enterology can dispute the importance of the emotional load affecting the alimentary tract and indeed it accounts for an appreciable proportion of all patients seen in hospital and at private consultations Emotional stress undoubtedly induces functional disorder particularly aerophagy and disturbance of the bowel rhythm but it is difficult to believe that it is a primary aetiological factor for organic conditions such as peptic ulcer and ulcerative colitis The influence of the emotions is perhaps better con sidered as an aggravating mechanism It seems probable that those who succumb to duodenal ulcers or ulcerative colitis have some constitutional or environmental factor present as well as the emotional stress which undoubtedly contributes to so many of the cases A vicious circle seems to be engendered from the uncertainty of life resulting from the illness and this induces more nervous tension The increase in emotional stability after a successful partial gastrectomy or colectomy indicates the importance of the somato psychic element In clinical practice it is of course essential to consider the anxiety factor most carefully in every case and many patients are greatly benefited if the physician can restore their perspective

With the basic sciences there is still much to be learnt about secretion and motility In Chapter 1 Bulbring describes some of the fundamental mechanisms concerned with smooth muscle activity of the intestines and perhaps this work will link up with the biochemical studies of Pernow and the role of polypeptide substance P which is a potent smooth muscle stimulating compound causing increased motility It is possible that the continual release of this substance gives the necessary tonic background for rhythmic activity facilitating the peristaltic reflex

Gastro enterology remains part of general medicine and surgery and represents indeed too big a proportion of general work ever to allow it to become an inde pendent speciality In other words one does not envisage a department of gastro enterology in every hospital Nevertheless there is scope and need for a certain number of departments where special facilities can be provided for the clinical and laboratory studies of gastro enterological problems A number of such depart ments have been opened during the past decade and are responsible for the increas ing momentum in the study of this sub-speciality of medicine and surgery

The production of such a volume is the result of teamwork not only by the con tributors but also by the staff of the Medical Department of Messrs Butterworth & Co and I wish to pay tribute to the efficiency courtesy and helpfulness of their medical department

*London November* 1957 F AVERY JONES

# INTRODUCTION TO THE FIRST SERIES

THE PURPOSE OF THIS BOOK is to bring together recent work in the gastro entero logical aspects of medicine and surgery In many countries as in Great Britain gastro enterology is not an established speciality such as cardiology or neurology but remains within the sphere of general medicine and surgery This book is therefore not written only for gastro enterologists but for physicians and surgeons interested in this field Each section has been undertaken by someone who has made a recent contribution to the particular subject for such contributors are best able to present an up to date account of their subject with recent progress given its correct perspective

Even with a large volume it is not possible to give space to every aspect of the subject and it makes no claim to be completely comprehensive Those fields in which there has been most progress are best represented as for example the oesophagus liver diseases and peptic ulcer

Gastro enterology has a greater number of unsolved aetiological problems than any other system of the body In addition to bringing together modern knowledge an attempt has been made also to represent growing points of research from which important clues may be contributed to major unsolved problems such as peptic ulcer For example the mechanism of secretion of acid by the stomach and vascular anatomy of the stomach are not sections with such intrinsic appeal to the clinician as the anaemias of the alimentary tract Nevertheless they present recent work which may prove of great importance There is a particular need for more research workers to be attracted to gastro enterology and it is hoped that this publication may have some influence in this direction

Close collaboration between physicians and surgeons is particularly needed in gastro enterology and this is well reflected in the list of contributors The application of existing knowledge to the practical management of for example ulcerative colitis is possible only if physicians and surgeons are willing to work together preferably leaving the patient in one ward No apology is offered for introducing some details of surgical technique where it has been thought desirable It is hoped that thereby the surgical reader may be given valuable practical points not readily available elsewhere and it is not without interest for the physician to have some impression of modern surgical methods

This publication is essentially representative of British and Australian work in gastro enterology Much valuable work has been done in recent years in America where gastro enterology has clearly been separated from general medicine and surgery as a distinct speciality Such American work has however been adequately brought together in recent publications and has been more readily available hitherto than corresponding British work

I wish to express my best thanks to the Medical Department of Messrs Butter worth & Co for the great help they have given me

F AVERY JONES

*London* 1952

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*The contents of this present volume is quite independent of that in the first series and the two books should be regarded as companion volumes*

CONTENTS OF THE FIRST SERIES

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# CHAPTER 1

# SMOOTH MUSCLE OF THE ALIMENTARY TRACT

EDITH BÜLBRING

## INTRODUCTION

THE muscular activity of the gastro intestinal tract shows many different patterns which have been classified under two main headings commonly known as (1) pendular movement and (2) peristalsis The former consists in a rhythm of short lasting contractions recurring almost with the regularity of the swing of a pendulum and these are generally believed to be of myogenic origin Peristalsis on the other hand implies the propulsion of the intestinal contents in response to increased filling of the lumen and this requires the participation of a nervous reflex A strict division of the two kinds of movement performed by visceral muscle is however not possible because increased filling of the lumen usually also stimulates pendular activity

## NERVOUS REFLEX ARC IN PERISTALSIS

The peristaltic reflex that is the propulsion of the intestinal contents in response to distension can be demonstrated very clearly in an isolated loop of ileum from the guinea pig The exact nervous pathway involved is still unknown Hitherto no histological evidence is available to decide whether a true reflex arc or an axon reflex is involved nor to what extent the extrinsic nerves participate It is established that afferent impulses from stretch receptors in the wall of the stomach travel up the vagus (Paintal 1954 Iggo 1955) but from studies on the distribution of vagal fibres which have been shown not to extend beyond the duodenum it is not likely that these stretch receptors are involved in peristalsis (Schofield 1957)

After cutting both vagi and splanchnic nerves and allowing them to degenerate (Gregory 1946 1947 Alvarez 1950) the propulsion of the contents through the intestinal tract still proceeds though it may be somewhat impaired Recent experiments on isolated loops of intestine have shown that the peristaltic reflex evoked by distension is quite normal after degeneration of all extrinsic nerves but that it is abolished after removal of the mucous membrane This indicates that the entire reflex arc is intrinsic and that the sensory distension receptors are situated in the mucosa

The crucial experiment—that is the removal of the intramural nerve plexus leaving both muscle coats intact—is not possible but the peristaltic reflex can be abolished by pharmacologically active substances which block some part of the reflex arc supposed to be involved This can be achieved by substances which block nervous conduction such as cocaine and other local anaesthetics It can be achieved by substances which block the synaptic transmission of the sensory impulses to the motor neuron such as hexamethonium and also by substances which block the action of the transmitter such as atropine which antagonizes the action of the parasympathetic mediator acetylcholine on intestinal smooth

central nervous system intact it maintains a tone which depends on a self regulating mechanism due to the sensory stretch receptors or muscle spindles situated within the muscles These register changes in muscle length and signal them to the central nervous

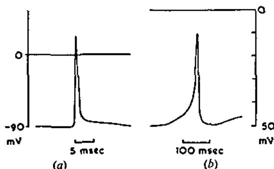



FIG 1 —(a) Intracellular record of action potential in skeletal muscle of the frog and (b) in intestinal smooth muscle of the guinea pig

system by the simple device of changing the frequency of impulses which they emit This information is passed on to the motor neuron whose activity on which the muscle tone depends is thus controlled Isolated skeletal muscle is unable to respond to stretch nor is it able to maintain a tone it is in a resting state

On the other hand the behaviour of intestinal smooth muscle is entirely different It is never resting neither in the body nor when it is isolated but it is in a continuous state of activity it changes its length spontaneously by a factor of 2–4 and similarly produces a very variable tension Its tone is to some extent influenced by the central nervous system but not exclusively controlled by extrinsic nerves nor is the tone entirely dependent on the enteric nervous system The muscle has thus some regulating mechanism of its own

## TRANS MEMBRANE POTENTIAL OF INTESTINAL SMOOTH MUSCLE

For the experiments to be described below the longitudinal muscle of the colon in the guinea pig the *Taenia coli* has been used throughout When a micro elec trode is inserted into this smooth muscle the trans membrane potential recorded is always lower than that of skeletal muscle

While the resting potential in skeletal muscle varies from fibre to fibre by only a few millivolts above or below 90 millivolts the membrane potential of intestinal smooth muscle fibres ranges from 20 to 80 millivolts with an average of 50 milli volts This enormous scatter is probably only partly due to the very small size of the cells (2–10 $\mu$ in diameter) which may be damaged more frequently than the much larger skeletal muscle cells It has however been found that the membrane potential is related to the muscle length and to the tension which it produces This will be more clearly understood after discussing another difference between smooth and striated muscle which is that in resting skeletal muscle the membrane potential is very stable at 90 millivolts while in smooth muscle no true resting potential can be determined because the muscle is continuously active The membrane potential is unstable it fluctuates and superimposed there is a rhythmic discharge of action potentials These spikes (Fig 1*b*) are smaller than the action potential of striated muscle they vary in size from a few to about 40 millivolts

muscle Yet these pharmacological measures are often inconclusive (Ambache 1955) for example it is not possible to abolish vagal effects entirely by atropine

## MUSCULAR RESPONSE TO STRETCHING

Considering the response to stretching one has to remember that intestinal muscle which has been deprived of all nerve cells—for example the isolated chronically denervated and plexus free circular coat of the intestine of the cat (Evans and Schild 1953)—still responds to distension by increasing its contractions Thus the muscular wall of the intestine responds to stretch and contracts to over come the extension irrespective of whether nervous elements are present or not How this is possible can be understood more clearly when the properties of the smooth muscle itself are examined

## ELECTRICAL POTENTIALS AND IONS

Recent advances in our knowledge have only been possible by using new methods which have been developed for the study of the properties of nerve and skeletal muscle and which have led to the present conception of the mechanisms involved in the activity of excitable tissues This conception (Hodgkin 1951) is based on the fact that the ionic composition of the tissue is different from that in the extra cellular fluid the potassium concentration being greater inside the cells while the sodium and chloride concentration is greater outside The electrical potential due to this difference in ionic concentration can be measured accurately by using intracellular electrodes (Ling and Gerard 1949) consisting of very fine glass capillaries with a tip diameter of about 0 1 μ filled with 3 molar potassium chloride which can be inserted through the cell membrane into the interior of a muscle fibre

In the resting state the trans membrane potential of skeletal muscle is about 90 milli volts the inside being negative with respect to the outside of the cell (Fig 1*a*) The resting membrane is almost impermeable to sodium and though some small leakage of ions along concentration gradients takes place an active metabolic process constantly pumps the sodium out of the cell and at the same time absorbs potassium into the cell (Hodgkin and Keynes 1955) In the active state there is a rapid movement of sodium and potassium ions across the cell membrane The electrical change associated with these movements is known as the action potential (Fig 1*a*) and is believed to be due to an initial increase of the membrane permeability to sodium ions followed by a delayed permeability to potassium ions Thus at first sodium ions enter the fibre at a rapid rate and as the sodium concentration is so much higher outside the membrane potential is reversed the outside becoming momentarily negative to the inside this is the rising phase of the action potential Soon potassium ions leave the fibres be cause the potassium concentration is so much higher inside and the membrane potential is restored this is the falling phase of the action potential The actual quantities involved in the movement of ions are exceedingly small Nevertheless the cell incurs a slight gain of sodium and a slight loss of potassium which if excitability is to be maintained has to be made good by the metabolic processes which remove surplus sodium out of the cell and take up lost potassium

## TONE

The behaviour of skeletal muscle at rest can be studied separately from that during activity It has a definite resting length and produces a definite maximal tension in response to a maximal stimulus In the whole organism with all connexions to the

Fig 3 shows the rising phase and the falling phase of such a small fluctuation taken with higher amplification and on a faster moving paper In the upper record it is clearly seen that a rise in tension results from the summation of individual increments in tension following each spike Then before the muscle tension reaches its peak the membrane potential rises the appearance of the spikes changes and the intervals between the spikes increase No longer is each one followed by an increment in tension so that the tension no longer summates and thus the muscle relaxes this phase is shown in the lower part of the record



Fig 3—Spontaneous changes in membrane potential spike frequency and tension Continuous record showing rising tension in upper part and falling tension in lower part (*Figs 3 4 6a 8 9b are reproduced by courtesy of the Editors of the* J Physiol )

The response of smooth muscle to extension is obtainable in the presence of the various pharmacological agents mentioned earlier which would block any nervous reflex arc It is thus a response of the smooth muscle fibre itself This cell combines the properties of a continuously discharging sensory organ with a contractile mechanism Such properties make the muscle eminently suitable for its role in the wall of a hollow organ the contents of which have to be mixed and moved along It does not require a nervous control mechanism via the central nervous system for the regulation of its tone The muscle s extensibility and at the same time its inherent mechanism by which it registers quantitatively the degree of extension enable it to react by producing a proportional degree of tension It is the change in membrane potential which determines the change in spike frequency and which is thus proportional to the tension This is particularly clear during the release of a previously stretched muscle which leads to a rise in membrane potential slowing or cessation of the spike discharge and sudden muscular relaxation An experiment in which the muscle was first stretched in steps of 5 millimetres and then gradually released is illustrated in Fig 4*a* The changes in membrane potential were only indirectly related to the muscle length (Fig 4*b*) but bore a straight line relation to the tension (Fig 4*c*) which the muscle produced actively in response to extension

## CORRELATION OF MEMBRANE POTENTIAL SPIKE FREQUENCY AND TENSION

The spontaneous pendular rhythm is probably due to intermittent stretch of adjacent groups of muscle cells which are arranged around a more or less distended intestinal lumen During this basic rhythm there is good correlation between the height of the membrane potential the rate of the spike discharge and the tension

causing only a partial depolarization of the membrane and hardly ever a reversal Whereas the action potential of skeletal muscle only lasts a few milliseconds smooth muscle spikes are of much longer duration They do not arise suddenly but are preceded by a slow depolarization gradually leading to the spike deflection This is an important characteristic common to tissues which are spontaneously rhythmically active For example the slow depolarization or pre potential is very marked in the pacemaker cells of the heart The fact that the prepotential is also seen in smooth muscle cells supports the view that the spikes are of myogenic origin and that each cell can be regarded as a pacemaker cell The average rate at which they discharge a spike is 1 per second but the frequency varies from 30 to 90 per minute (Fig 2)

## RESPONSE TO EXTENSION

As mentioned before intestinal smooth muscle is highly extensible and extension stimulates it to contract The question remains is this reaction muscular or is it due to a nervous reflex? When the electrical activity of the muscle is recorded the

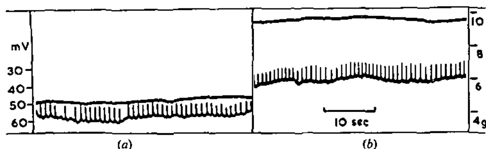



Fig 2—Record of tension and membrane potential showing spontaneous rhythm Between (a) and (b) the muscle was stretched from 8 to 10 millimetres

response to stretch is seen to be two fold there is a fall in membrane potential and an increase in the rate of discharge of spike potentials The most likely explanation is that the stretch causes deformation of the muscle cells this leads to a change in membrane permeability and the depolarization which ensues is the cause of an increase in spike frequency Now the spike frequency is directly related to the tension because each spike is followed by a small increment in tension Thus when the muscle is stretched it is depolarized the rate of its spontaneous spike discharge increases and its tension rises in proportion (Fig 2) The two records show the muscle tension together with the membrane potential and the rhythmic spike discharge recorded from one muscle cell The response to stretch from 8 millimeters (first record) to 10 millimetres (second record) consists in a fall in membrane potential *from 60 to 40 millivolts a rise in spike frequency from 60 to 74 per* minute and an increase in tension from 5 to nearly 10 grammes

## SPONTANEOUS ACTIVITY

Apart from these gross changes produced by extension there are smaller spontaneous fluctuations in both records Neither the tension nor the membrane potential is maintained at a steady level nor is the spike frequency completely regular Periods of faster discharge alternate with periods of slower activity

## ELECTRICAL AND PHARMACOLOGICAL EXCITATION AND INHIBITION

There are two further ways by which the close correlation between membrane potential spike frequency and tension can be demonstrated The first consists in altering the electrical potential by applying to the outside of the cells electrotonic currents The second consists in applying pharmacologically active substances which depolarize or hyperpolarize the membrane The application of an anodal current to the outside of the cell increases the trans membrane potential while a cathodal current has the opposite effect it reduces the positive charge on the outside and diminishes the trans membrane potential This depolarization stimu

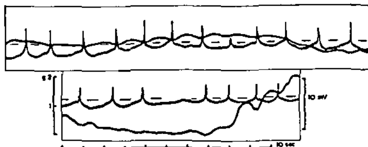


FIG 5 —Spontaneous pendular activity Tension and membrane potential are recorded The production of tension depends on the spike frequency The discharge occurs at an approximately constant level (broken line) and the distance between the height of this level and that of the membrane potential determines the extent of the prepotentials and thus the spacing of the spikes

lates the muscle increasing both its electrical activity and its tension whereas anodal polarization depresses the muscle causing slowing or cessation of electrical activity and relaxation

The nature of excitation and inhibition can be understood when it is realized that the changes produced are not as they are in skeletal muscle—from rest to activity or vice versa—but that a basic moderate activity is changed in degree This is illustrated in Fig 6*a* where initially the muscle is moderately active and where the excitatory effect of cathodal polarization—a rise in spike frequency and tension—is immediately annulled by the inhibitory effect of anodal polarization that is simply by reversing the polarity It is actually possible to imitate the spontaneous fluctuations by applying weak polarizing currents and reversing the polarity once or twice per minute Antagonistic pharmacological effects appear to be the same as those produced by opposite electrotonic currents Adrenaline (*see* Fig 10*a*) like anodal polarization decreases spike frequency and tension while histamine and acetylcholine depolarize and increase spike frequency and tension Fig 6*b* shows the effect of histamine to be compared with that of cathodal polarization in Fig 6*a* The change in electrical activity in response to acetylcholine is shown at a higher amplification and a faster time base in Fig 7

## POTASSIUM EXCHANGE

If the conceptions derived from the observations on skeletal muscle and nerve which have been described above are applied to smooth muscle one would expect

periods of low membrane potential rapid spike discharge and high tension alternate with periods when the membrane potential rises spike frequency slows and the muscle relaxes It is not surprising therefore to find a large scatter of values when the membrane potential is measured in successive fibres because it depends on the state of the cell that is on the degree of its activity at the moment when the micro electrode is inserted and fundamentally the degree of activity is determined by the extent to which the preparation has been stretched

The reaction of a continuously discharging sensory organ to outside influences consists in a change of the rate of discharge and in the smooth muscle of necessity this results in a change of tension The rate of discharge depends on the height of the membrane potential This is illustrated in Fig 5 which shows the spontaneous changes in the state of a cell and how the spacing of the spikes is determined by the extent to which the pre potential has to proceed before a level (indicated by the broken line) is reached at which a spike arises At first with a high membrane

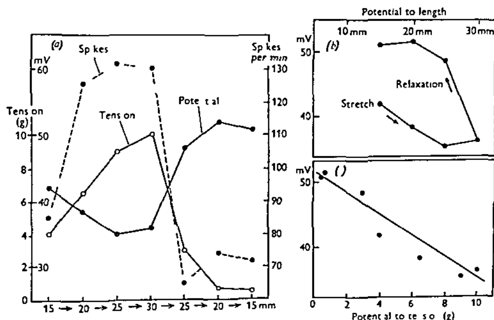



FIG 4 —Stepwise stretch and release (*a*) are associated with changes in potential spike frequency and tension Potential changes are not directly related to muscle length (*b*) but to the tension which the muscle produces (*c*) as a reaction to extension

potential the pre potential has to proceed a long way before a spike is initiated but when the potential falls the pre potential has to cover a shorter distance until the spike deflection occurs thus spikes arise more frequently and the tension rises At the end of the upper record as the membrane potential increases and the pre potentials are once more prolonged the muscle relaxes The continuation in the *lower record* shows the fall in tension as spike discharge stops and another rise in tension resulting from a faster spike discharge

A more powerful effect can be obtained by a pharmacological depolarizing agent such as histamine It causes a large increase in spike frequency and tension (Fig 9*a*) with a greatly augmented rate of loss of potassium (Fig 9*b*) It has also been demonstrated that stretch to which the muscle offers an active resistance by producing a tension leads to an increased rate of loss of potassium

Naturally during recovery the loss incurred during activity has to be replaced by the metabolic processes mentioned above The time resolution of methods measuring the rate of uptake of radio active potassium is not sufficient to show rapid changes but if the muscle is kept in a relaxed state by depressing its activity

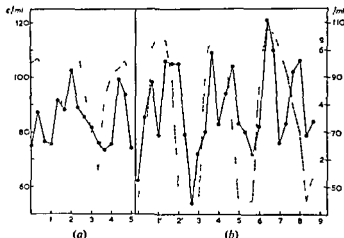



FIG 8 —Spontaneous pendular rhythm Record of tension (broken line) and the rate of loss of potassium (continuous line) (*a*) in the absence (*b*) in the presence of atropine

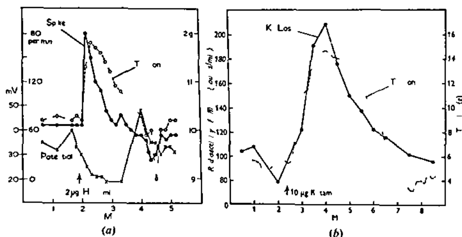



FIG 9 —The effect of histamine (*a*) on the membrane potential spike frequency and tension (*b*) on the rate of loss of potassium from the muscle associated with the production of tension

that during the periods of depolarization when the rate of spike discharge is rapid and the tension increases the muscle would lose potassium at a greater rate than during the periods of lesser activity and relaxation This can be tested by using radio active tracers for example $^{42}K$

The muscle is loaded by soaking it in a solution containing radio active potassium until much of its intracellular potassium has been exchanged with radio active potassium It is then washed with non radio active solution and the rate of loss of potassium is measured by the appearance of radio activity in the washing solution

Using this method it has been possible to show that the rate at which potassium is lost from the muscle is increased when the tension rises and that it is decreased when the muscle relaxes Even the relatively small changes in tension taking place during pendular activity can be shown to be associated with parallel fluctuations in the rate of loss of potassium from the muscle (Fig 8)

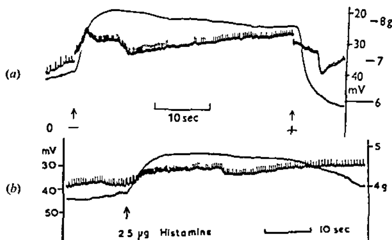



FIG 6 —Depolarization (a) by cathodal (−) current stimulation causes increased electrical activity and rise in tension Reversal of polarity (+) causes inhibition The effect of histamine (b) is similar to (a)

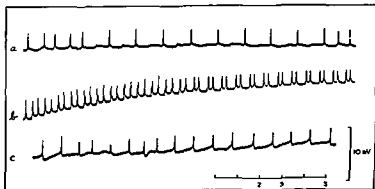



FIG 7 —The effect of 5μg acetylcholine on the spontaneous spike discharge (a) before (b) during and (c) after (*Reproduced from* Gastroenterologia *by courtesy of S Karger Basle*)

can be stimulated uniformly along its whole length by placing the electrode inside the lumen along its axis Single shocks then stimulate the post ganglionic cholinergic nerves and the muscle fibres contract in unison This is for example what happens when impulses arrive along the vagus nerve at the nerve endings acetylcholine is liberated and thus all cells are simultaneously exposed to the depolarizing action of the parasympathetic transmitter Conversely when impulses arrive along sympathetic nerves adrenaline and nor adrenaline are liberated and all the cells are exposed to the hyperpolarizing action of the sympathetic transmitter The situation is complicated by the fact that the vagus nerve contains not only chol inergic but also adrenergic fibres (Paton and Vane 1956) and that cholinergic as well as adrenergic ganglia are present in the wall of the intestine (Ambache 1951)

## CONCLUSION

The nature of gastro intestinal motility is thus very complex but it can be under stood if one realizes that it is the result of the integrated activity of three different regulating mechanisms Two of these are nervous and consist first in the extrinsic sympathetic and parasympathetic innervation and secondly in the intrinsic nerve plexus The third is the smooth muscle itself whose behaviour appears to be due to the instability of its membrane This leads not only to auto rhythmicity but enables the muscle to react like a continuously discharging receptor organ to various stimuli chemical or mechanical by changing its rhythm The frequency of the rhythmic discharge—and therefore of the tension which the muscle produces—is determined by the height of the membrane potential At a low membrane potential the cells are automatically very active while at a raised membrane potential they are less ready to discharge impulses Thus it depends very largely on the initial state of the muscle cell whether a stimulant or inhibitory nerve impulse will be effective It is therefore not surprising that in different experimental conditions various workers have obtained contradictory results and that they could not distinguish strictly between purely muscular responses and those involving nervous interaction particularly as the transmitter substances merely increase or decrease the automatic motility and modify its pattern

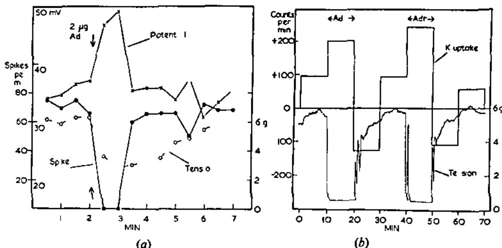
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with adrenaline it can be shown that during this period of inactivity the rate of uptake of potassium into the muscle is greater than during the control periods The effect of adrenaline on intestinal smooth muscle is inhibitory Adrenaline raises the membrane potential and stops the spike discharge consequently the muscle tension falls (Fig 10*a*) The rate of uptake of potassium is measured (Fig 10*b*) by the following method

A muscle is exposed to a solution containing radio active potassium for 5 minutes it is then washed for the next 5 minutes with normal inactive solution to wash out extracellular spaces and during the last minute of such a 10 minute period the radio activity in the muscle is determined This procedure is continued until the time at which the radio activity of the muscle is maintained near a steady level (zero line in Fig 10*b*)

If now during one such period of 10 minutes the muscle is relaxed by exposure to adrenaline the muscle takes up more potassium than during control periods Thus adrenaline appears to stimulate those reactions which take place during recovery when the ionic concentration inside the muscle fibres is restored




(*a*) (*b*)

FIG 10 —The effect of adrenaline (*a*) on the membrane potential spike frequency and tension (*b*) on the rate of uptake of potassium by the muscle associated with relaxation

## CONTRACTILE MECHANISM

There is at present no information available about the link connecting the events taking place at the membrane with the contractile mechanism but it is clear that any contraction observed in smooth muscle is comparable with a tetanus of striated muscle The tension produced is directly proportional to the spike frequency because if the rate is fast the mechanical changes following each spike summate and the total tension rises If on the other hand the rate of spike discharge is slow the mechanical changes following each spike no longer summate and the tension remains stationary or falls Synchronization of a large number of fibres has to be achieved if an effective change of tension is to be produced When pharmaco logical agents or electrotonic currents are applied synchronization is probably due to a uniform change of the membrane potential in all cells Paton (1954) has shown that in an isolated piece of intestine the muscle of the intestinal wall

## MOUTH AND PHARYNX

**Moniliasis**

Moniliasis occurs in about 10 per cent of patients treated with ACTH and cortisone and it is almost as common in patients treated with the hormones alone as in those treated with hormones together with antibiotics (Bratlund and Holten 1954)

In typical cases the mouth the pharynx and the larynx are involved with consequent dysphagia and aphonia The lesions may spread down the trachea and into the lungs and the organisms may be found in the stools but it is debatable whether they actually infect the intestine Generalized skin rashes or moniliids may appear Local treatment consists of careful oral hygiene mouth washes of saturated sodium bicarbonate solutions and painting with gentian violet or Mercurochrome For general treatment Nystatin (Mycostatin) and hydroxystilbamidine have been used but the lesions are often resistant Nystatin is given by mouth in a dosage of 500 000 units thrice daily Hydroxystilbamidine is given by continuous intravenous drip dissolved in 200–300 millilitres of 5 per cent dextrose or normal saline solution The dose recommended for adults is 3–5 milligrams per kilogram of body weight daily or on alternate days Other drugs recommended for fungal infections but probably not very effective are *p* hydroxybenzoic acid and fatty acids If the infection is mild the hormone therapy may be continued but if it is severe it should be suspended

**Sjogren s syndrome (keratoconjunctivitis sicca)**

Improvement has been seen in Sjogren s disease following treatment with ACTH and cortisone with subsidence of the swelling of the glands return of secretion and disappearance of malaise Not all cases respond however and in the later stages of the illness the lesions are probably irreversible (Ehrlich and Greenberg 1954 Gaulhofer 1954)

**Scleroderma**

Scleroderma may involve any part of the alimentary tract but particularly the oesophagus and the colon experience has shown that the results of treatment with ACTH and cortisone have been disappointing

## PEPTIC ULCER

When Selye (1936) first described the alarm reaction he noted acute gastro intestinal ulcers stimulation of the adrenal cortex and involution of the thymus and lymphatic tissues He found that gastro intestinal ulcers still occurred in animals from which the adrenals had been removed and therefore they were not dependent upon an excess of adrenocortical hormones These observations should be borne in mind nowadays when there is perhaps too great a tendency to attribute gastro intestinal ulceration to over activity of the adrenal cortex It is probable that an excess of adrenal hormones does not actually cause peptic ulcers but it sensitizes the gastro duodenal mucosa to stimuli which might otherwise be harmless (Engel 1955)

Soon after the introduction of ACTH and cortisone into therapeutics it was observed that their administration in man was followed by a rapid increase in the excretion of uropepsinogen in the urine (Gray et al 1954) Increases were of the

## CHAPTER 2

# THE EFFECTS OF ACTH AND CORTICOSTEROIDS ON THE ALIMENTARY TRACT

L J Witts

## INTRODUCTION

The pituitary gland controls the activity of the adrenal cortex by the secretion of corticotrophin or ACTH Under the stimulus of ACTH the adrenal cortex pours out three different types of hormones the gluco-corticoids the mineralo corticoids and the androgenic hormones

The gluco corticoids of which cortisone is an example are the hormones which are used up in the so called alarm reaction or reaction to situations of acute stress The therapeutic effect of cortisone and similar gluco-corticoids depends on their ability to alter the reaction of the body to noxious stimuli and in particular to decrease the inflammatory response

The mineralo corticoids promote the retention of salt and the androgenic hormones in excess produce virilism in the female

The three groups of hormones are closely related and overlap in activity Apart from this we are not specially concerned in gastro enterology with the mineralo-corticoid and androgenic effects of ACTH and the adrenal hormones This chapter will therefore be devoted to the effects on the alimentary tract for good or ill of the anti inflammatory and anti stressor actions of these hormones

### Methods of administration

ACTH may be used either in the form of the soluble short acting preparation or as the gel which is long acting Both preparations may be given subcutaneously or intramuscularly When a prompt and maximal effect is desired soluble ACTH can be given by intravenous drip The gluco-corticoids which have most been employed are cortisone acetate which is usually given by mouth in tablets of 25 milligrams and hydrocortisone acetate which is used for local application Hydrocortisone is also prepared in the form of the free alcohol and the hemi succinate either of which may be employed for systemic or topical application Recently cortisone acetate is tending to be displaced in the treatment of alimentary disease by prednisone (dehydrocortisone) and prednisolone (dehydrohydrocortisone) which are given by mouth in tablets of 5 milligrams a dose of 5 milligrams being approximately equivalent to 25 milligrams of cortisone acetate The advantage of prednisone and prednisolone is that with ordinary doses there is no disturbance of the electrolyte balance and it is not necessary to prescribe a salt free diet and a supplement of potassium salts Until we have more experience of prednisone and prednisolone caution must be used in extrapolating to them experience gained with cortisone and hydrocortisone

hope that they might promote healing and only a small proportion have had exacerbations Indeed a striking case has been reported by Deutsch et al (1956) in which ACTH was used successfully in the treatment of recurrent massive gastro intestinal haemorrhage following subtotal gastric resection in a patient whose gastric mucosa exhibited easy bleeding and friability of tissue

Sandweiss does not believe that peptic ulcer is an absolute contra indication to the administration of ACTH and corticosteroids though he advises great caution Apart however from the small doses required in hypopituitarism and Addison s disease ACTH and corticosteroids should not be prescribed in the presence of a peptic ulcer or of a history of ulcer unless their use is obligatory In other words they should not be prescribed for patients with rheumatoid arthritis or ulcerative colitis with a history of peptic ulcer Some disastrous accidents have been observed in ulcerative colitis where this prohibition has been disobeyed Occasionally it may be necessary to try to prevent complications when their use is imperative In one patient with gastric ulcer and an idiopathic acquired haemolytic anaemia in whom death seemed inevitable if cortisone were not continued a partial gastrectomy was performed and the drug was then given without incident

Gastric and duodenal ulceration in patients taking ACTH or corticosteroids is often asymptomatic haemorrhage may occur without warning and perforation may not give the usual symptoms If there is any epigastric distress during corticoid therapy aluminium hydroxide and alkalis should be given—indeed some physicians prescribe them as a routine when prednisone and prednisolone are used—and the possibility of peptic ulcer should be seriously considered

## HEPATITIS

The information to hand on the effect of ACTH and cortisone on experimental injury or inflammation of the liver is confusing No clear evidence of benefit has been obtained In acute hepatic failure in rats produced by the injection of small quantities of carbon tetrachloride into the mesenteric vein Reynell (1955) found that cortisone failed to reduce the mortality Similarly in chronic carbon tetrachloride poisoning in rats Aterman and Ahmad (1953) found greater deterioration of liver function and more widespread liver damage in animals treated with cortisone than in the controls

In acute hepatitis in man ACTH and cortisone produce a prompt and dramatic fall in serum bilirubin and they speed up the return of other clinical laboratory and pathological features to normal However relapse is more frequent in patients so treated than in controls possibly because of disturbances in the virus host relationship which hinder the development of immunity (Evans et al 1953) The hormones therefore are not advisable in the average case of viral hepatitis but they may be tried when there is progressive hepatic destruction and coma appears imminent They are most likely to be helpful in subacute or recurrent hepatitis The value of the hormones in cirrhosis in man is dubious Sklar and Young (1955) have reported 10 cases of coma or impending coma in advanced portal cirrhosis treated with cortisone or ACTH all of whom died although there was the usual fall in serum bilirubin They commented on the absence of the usual euphoric effect of the hormones although other authors have claimed that this can be obtained and is of value in cirrhosis

order of 100 per cent and they closely followed the changes in ketosteroid excretion This did not happen in patients with pernicious anaemia or after total resection of the stomach and it was clear that the uropepsinogen was derived from the zymogenic cells of the stomach Examination of the gastric juice showed a similar increase in the acid and pepsin of the basal and nocturnal secretion though this came a little later and might take 7–14 days to reach its maximum which was of the order of 100–400 per cent Thus part of the early increase in uropepsinogen was probably due to changes in the renal threshold and though the excretion of uropepsinogen in the urine mirrors the secretion of acid and pepsin in the stomach the reflection is not exact Removal of the gastric antrum and vagotomy do not alter the response It was also noted that there was a fall in the viscosity of the gastric juice as well as a decline in the visible mucus (Hirschowitz et al 1955)

A review of the older literature and the collection of fresh data showed the close connexion between the thalamo pituitary adrenocortical mechanism and the secretory capacity of the stomach Increases in the excretion of uropepsinogen follow the stress of pain trauma surgery myocardial infarction burns and strong emotions The gastric secretion is depressed in Simmonds s disease and Addison s disease and is restored to normal by cortisone It is often increased in Cushing s syndrome and is restored to normal by adrenalectomy Kyle et al (1956) suggest that even in patients without endocrine disease there is some correlation between the level of gastric secretion and the quantity of ketosteroids excreted in the urine but other workers have found no evidence that adrenocortical activity as measured by appropriate physiological and chemical tests is increased in patients with peptic ulcer

Exacerbation of existing ulcers and the appearance of fresh ulcers of the stomach and duodenum with haemorrhage and perforation are not uncommon in patients treated with ACTH and cortisone these hormones are equally culpable in this respect It is possible that ulceration is more common after prednisone and prednisolone but this may be a corollary of their greater potency (Bollett et al 1955) It was at first thought that the ulceration was the result of an increase in the gastric secretion but this is a little doubtful Ulceration is equally common in patients with and without a history of peptic ulcer and it may occur before the rise in hydrochloric acid and pepsin which may be delayed until the end of the second or third week At operation or necropsy many of the ulcers have been found to be recent or acute At times they are much larger than the usual peptic ulcer and they resemble the acute ulcers of the alarm reaction

Some useful figures have been collected by Sandweiss (1954) Of 50 cases recorded in the literature of ulceration following hormone therapy 22 were duodenal ulcers 12 gastric and 2 stomal Nineteen bled 11 perforated and 4 did both 9 out of the 50 patients died Of 500 patients given short term treatment with ACTH or cortisone for conditions other than peptic ulcer 1 patient developed a peptic ulcer and 8 suffered activation of existing ulcers Of 480 patients on long term treatment with these substances 25 either developed new ulcers or suffered reactivation of old ones Many of these patients were suffering from rheumatoid arthritis About 6–8 per cent of rheumatoid patients have a history of ulcer and a number might be expected to break down during any particular period of observation even without ACTH or cortisone Moreover ACTH and cortisone have been deliberately given to a considerable number of patients with peptic ulcer in the

lymph nodes and the tunica propria of the mucosa of the small intestine these macrophages apparently contain a glyco protein and they are stained by the periodic acid Schiff reagent Whipple s disease differs clinically in the preponderant incidence in males onset in middle life and frequent presence of fever raised erythrocyte sedimentation rate pigmentation migratory arthritis and polyserositis The diagnosis can sometimes be confirmed by biopsy of a peripheral lymph node showing the typical glyco protein Treatment had hitherto been uniformly un successful with a fatal termination 1–5 years after the onset of the illness

The pigmentation hypotension asthenia and low 17 ketosteroid excretion have suggested adrenal hypocorticism though they are probably secondary to the wasting and there is a normal response to ACTH A more cogent reason for expecting benefit from ACTH and corticoids is the resemblance to one of the collagen diseases of such features of the illness as the fever raised erythrocyte sedimentation rate arthritis and polyserositis Although 59 cases of Whipple s disease had been reported in the world literature at the time of writing information is available for only 9 cases treated with ACTH or corticoids (Puite and Tesluk 1955 Wang et al 1956) Two of these cases died but 7 showed remarkable improvement with disappearance of all symptoms of ill health in some Relapse is likely to occur unless the treatment is maintained but contrarily it has also been known to occur despite continued therapy In patients who have come to autopsy within a month of starting treatment no change has been seen in the pathological process of intestinal lipodystrophy It is not yet known whether prolonged treat ment will result in mobilization and removal of the glyco protein from the foam cells

## ULCERATIVE COLITIS AND REGIONAL ILEITIS

The chief interest to gastro enterologists of ACTH and the corticoids lies in their application to the treatment of ulcerative colitis and regional ileitis Other methods of treatment of these two diseases medical and surgical have well known dis advantages and disappointments Both diseases are of unknown aetiology but in ulcerative colitis the nature of the colonic inflammation and the occurrence of skin rashes and arthritis have suggested that the disease might be a manifestation of hypersensitivity allergic disorders are known to respond frequently to the hormones and therefore ileitis and colitis might equally well do so The hormones are non specific anti inflammatory and euphoric agents and might therefore be expected to produce local and general improvement quite apart from hyper sensitivity

On the other hand the hormones are known to impair healing and the resistance to infection There is therefore a danger that they may provoke haemorrhage perforation abscess formation giant ulceration and bacterial and fungal infections In contrast to rheumatoid arthritis ulcerative colitis is often made worse by pregnancy though the exacerbations commonly occur either in the first trimester or after parturition not in the second and third trimester when the titres of steroid hormones are at their highest (Crohn et al 1956)

In regional ileitis there is usually much cicatrization which affects the entire intestinal wall the regional lymph nodes and the mesentery in ulcerative colitis the damage although severe is surprisingly superficial being restricted to the

With ACTH and cortisone there is considerable risk of increasing water retention in disease of the liver but this may be avoided by the use of prednisone and prednisolone

## STEATORRHOEA

In 1936 Verzar and McDougall claimed that the excretion of fat in the faeces of rats increased after extirpation of the adrenal glands This finding has not been altogether corroborated by subsequent workers and although there are superficial resemblances between sprue and Addison s disease as there are between pernicious anaemia and Addison s disease—pigmentation asthenia disturbed absorption of water—there is in fact no evidence of primary depression of the adrenal cortex in steatorrhoea The effects of ACTH and corticoids in this disorder therefore are not due to supplying a deficiency but are pharmacological

There is now no doubt of the therapeutic value of ACTH and corticoids in the steatorrhoea of sprue coeliac disease and idiopathic steatorrhoea Initial failures were due to inadequate dosage or insufficient duration of treatment The response is as follows Fat absorption improves diarrhoea disappears there is an increased sense of well being appetite improves and weight is quickly gained The abnormal radiological findings in the small intestine—the so called deficiency pattern—return to normal There may or may not be a time lag in the response to therapy In idiopathic steatorrhoea fat absorption does not revert completely to normal and relapse occurs within a few days or weeks if the treatment is interrupted The treatment is of particular value in severe cases where the debilitating watery diarrhoea can often quickly be checked

The mode of action of the hormones is not entirely clear they probably subdue the inflammation of the mucous membrane which is now believed to occur in many cases of steatorrhoea they improve peristalsis and increase the appetite The absorption curves of glucose vitamin A iron and vitamin $B_{12}$ have all been shown to be improved (Drenick et al 1955 Glass 1956 Kelley et al 1955) There is a rise in serum calcium and serum proteins a return of the prothrombin time to normal and an increase in chylomicron counts after fatty meals The faecal nitrogen as well as the faecal fat decreases and anaemia improves Unfortunately experience suggests that both in primary and in secondary steatorrhoea the biochemical lesion may become irreversible in the later stages

In acute or severe cases treatment is best begun with ACTH—either ACTH gel 40–80 units once daily or an intravenous drip of 20 units of ACTH in 500 millilitres of physiological saline solution or 5 per cent dextrose repeated daily In debili tated cases *up to 40 units of intravenous ACTH may be required daily Later it* should be possible to change over to one of the corticoids by mouth Maintenance doses of cortisone have commonly been of the order of 37 5–50 milligrams daily The equivalence of the various corticoids in steatorrhoea has not yet been estab lished and presumably depends on their absorbability Adlersberg et al (1953) in a careful comparison in 17 cases found that hydrocortisone acetate was not effective in chronic steatorrhoea but hydrocortisone free alcohol was effective

**Whipple s disease**

Whipple s disease or intestinal lipodystrophy differs in pathology from sprue and idiopathic steatorrhoea in the presence of Sudan negative macrophages in the

much change in the electrolyte balance It is doubtful whether there is any intrinsic difference between ACTH on the one hand and the corticoids on the other but in a sick patient it may be easier to obtain a quick effect with ACTH and then change to one of the corticoids Where doses larger than 37 5 milligrams a day of cortisone or its equivalent are given for any length of time occasional booster doses of ACTH should also be given to prevent adrenal hypoplasia for example 60 units of ACTH gel daily on 3 successive days each month

In patients treated with ACTH or cortisone 1 gramme of potassium chloride should be given 4 times a day provided it does not increase the diarrhoea A close watch should be kept on the blood chemistry although experience has shown electrolyte disturbances to be infrequent Estimation of the eosinophils in the blood and the 17 ketosteroids in the urine is unnecessary except where resistance to therapy or adrenocortical insufficiency is suspected Proctoscopy may usefully be carried out at intervals of 7–14 days

Dramatic improvement in symptoms may occur in 24–48 hours fever promptly subsides the clinical signs of toxaemia disappear the erythrocyte sedimentation rate returns to normal and there is a gain in weight The control of diarrhoea may be immediate or gradual bleeding may rarely persist up to 6 weeks Abdominal distress is quickly relieved The patient usually feels euphoric but this is by no means always the case Pre existing anxiety or depression may deepen and several cases of suicide have been recorded Suicide of course is not uncommon in patients with chronic ulcerative colitis and there is no evidence that it is more common in patients treated with the hormones

Objective improvement in the colon lags a good way behind the subjective improvement in symptoms In patients reaching the stage of complete remission the mucosa as seen through the sigmoidoscope returns to normal in 1–3 months It is important to note that a symptomatic remission may occur in a patient whose colonic mucosa is still inflamed such a remission is unstable Unfortunately even when the remission is complete the patient cannot be promised lasting recovery from the disease Radiological improvement is often inapparent or greatly delayed Nevertheless over a period of months or years pseudopolyps may resolve spasmodic strictures may open up and haustration may return

Some of the complications of hormone therapy have already been mentioned Treatment must often be pushed to the extent of producing Cushing s syndrome and this is distressing to the patient Electrolyte disturbances oedema glycosuria activation of peptic ulcer with haemorrhage or perforation and allergy to ACTH have all been noted More important in this context are the complications which are specially related to the treatment of ulcerative colitis Texter et al (1953) noted that whereas as a rule the oedema and the inflammatory reaction in the colonic mucosa rapidly subsided and the ulcers healed in patients with fulminating colitis treated with ACTH in some patients large coalescent punched out ulcers developed although the intervening mucosa was essentially normal Giant ulceration might occur longitudinal ulcers sometimes of great length their edges undermined and unaccompanied by significant fibrosis or mucosal regeneration Lesions of this kind are particularly liable to occur when therapy with corticoids is abruptly discontinued Haemorrhage and perforation may occur in patients treated with ACTH and corticoids and perforation may be clinically unrecognized exhibiting no sign except an unrelenting downhill course Whenever there is a

mucosa and submucosa of the colon in most cases (Warren and Sommers 1954) *A priori* then better results might be expected in ulcerative colitis than in regional ileitis and this indeed has proved to be the case Nevertheless even in chronic ulcerative colitis the odds against permanent cure are high Although the mucosa may appear superficially intact when the disease has reached the stage of remission microscopic examination shows a considerable alteration in the structural pattern (Lumb and Protheroe 1955) The mucous membrane is thinned and the regular arrangement of the crypts is lost The lamina propria may be oedematous with obstructed lymphatic vessels this being one reason why relapse is so likely to occur

Large series of patients have now been treated with ACTH and corticoids and it is possible to assess the immediate effects with considerable accuracy (Kirsner and Palmer 1954 Truelove and Witts 1954 1955) Much less is known about the long term effects and the value of maintenance therapy (Elliott and Giansiracusa 1954 Wirts et al 1954) Nevertheless it is already abundantly clear that ACTH and the corticoids are a valuable addition to the therapy of ulcerative colitis On occasion they may be life saving and they have greatly increased the freedom of manoeuvre in treatment The hazards attending their use have proved less formid able in practice than in theory It has not yet been shown however that the natural course of ulcerative colitis has been altered In regional ileitis the value of the hormones remains questionable The treatment of ulcerative colitis will first be discussed

Ulcerative colitis

Radiological examination of the chest should always be made before treating a patient with the hormones and if the history is at all suggestive of peptic ulceration a barium meal should be performed In a patient with active or arrested tubercu losis or with an active or healed peptic ulcer the possible benefit to be gained from hormone therapy should be carefully weighed against the real risk of activating these lesions It cannot be said that hormone therapy is absolutely contra indicated but certainly it must be carried out with extreme circumspection The usual basic treatment for ulcerative colitis is given—a bland diet with vitamin supplements sedatives and anti spasmodics and haematinics and transfusions as required Sulphonamides are probably of value and either Salazopyrin or a poorly absorbed sulphonamide such as sulphaguanidine may be used It is probably unwise to give antibiotics as a routine owing to the risk of fungal infections when a patient is receiving both antibiotics and corticoids If antibiotics are required because of intercurrent infection penicillin is probably the least harmful After a few weeks on any chemotherapeutic drug or antibiotic an intestinal flora develops which is resistant to it it is desirable therefore to keep one or more antibiotics in reserve (for example streptomycin) in case surgery becomes necessary

In very sick patients treatment may be commenced with an intravenous drip of ACTH Otherwise ACTH gel 40–80 units subcutaneously or cortisone 200–300 milligrams a day by mouth should be used It is important to begin treatment with an adequate dose which can be reduced when the disease is brought under control The equivalence of the various corticoids in ulcerative colitis has not yet been worked out but there is every reason to believe that hydrocortisone predni sone and prednisolone produce the same effects as cortisone when given in corresponding dosage and the two last named have the advantage of not producing

the stage of complete remission about 50 per cent unfortunately relapsed again within 2 years On the other hand the indications for surgery were broadened and many patients who would formerly have been too ill were now rendered fit for operation Elliott and Giansiracusa (1954) found that of 33 patients given short term hormone treatment 21 (63 7 per cent) went into remission but of these only 12 remained in remission at the end of 2 years

Truelove and Witts (1954 1955) with the help of a number of colleagues were able to organize a controlled trial of cortisone in ulcerative colitis The trial was a double blind one in that dummy treatment was given to 50 per cent of the patients and neither the physician in charge nor the patient knew whether the cortisone or the dummy was being given This was considered to be important on account of the influence of psychological factors on ulcerative colitis All patients were treated as if they were having cortisone so that suitable precautions could be taken in the event of complications developing The total number of patients was 210 of whom 109 received cortisone and 101 were controls Forty per cent of the patients were in their first attack the remainder were chronic or relapsed cases The results are shown in the Table

TABLE

RESULTS OF SHORT TERM TREATMENT WITH CORTISONE IN ULCERATIVE COLITIS

| | *First attacks* | | *Relapses* | |
|---|---|---|---|---|
| | *Cortisone group (per cent)* | *Control group (per cent)* | *Cortisone group (per cent)* | *Control group (per cent)* |
| Remission | 42 | 13 | 41 | 17 |
| Improved | 36 | 16 | 22 | 30 |
| No change or worse | 22 | 71 | 37 | 52 |

Both in first attacks and in chronic cases the percentage of remissions was over 40 in patients treated with cortisone as compared with 13 per cent and 17 p r cent respectively in the controls The total percentage improved (78) was higher in first attacks treated with cortisone than in any other group Severely ill patients did a good deal worse than those mildly ill but with every degree of severity there was a distinct advantage on the side of those treated with cortisone This is a finding of some importance as there had been dispute whether cortisone should be limited either to mild cases or to severe cases of the disease It is evident that all patients with ulcerative colitis may benefit from cortisone irrespective of the *severity of the disease There was no increase in complications* such as perforation and haemorrhage but pyogenic complications were rather more frequent The immediate mortality was 4 6 per cent in the cortisone treated group and 10 9 per cent in the control group

No maintenance therapy was given in this trial and the picture was less favour able when the results were reviewed 9 months to 2 years later In patients in their first attacks 35 per cent of those treated with cortisone had remained free from symptoms as compared with 13 per cent of the controls In chronic or relapsed

possibility of perforation auscultation over the abdomen for peristaltic sounds and radiological examination for free gas should be performed Distension may be due to potassium deficiency which may be revealed by the electrocardiogram as well as by biochemical *examination*

Local pyogenic complications around the rectum such as ischio rectal abscess and fistula in ano are more common in patients treated with the hormones as also are more remote infectious complications such as conjunctivitis iridocyclitis ulcerative keratitis furunculosis septicaemia and pyaemia One fatal case of bilateral massive adrenal haemorrhage similar to the Waterhouse Friderichsen syndrome has been described (Wilson and Roth 1953)

A complication which is of particular importance is relative adrenocortical insufficiency which may lead to intractable shock after major surgery sometimes even after minor surgical procedures This may occur a year or more after the suspension of corticoid therapy (Hayes and Kushlan 1956)

Whenever possible therapy should be changed to ACTH before performing ileostomy or colectomy and surgery should not be undertaken until there is a satisfactory response as shown by the eosinophil count and the ketosteroid excretion In an emergency an intravenous drip of ACTH or parenteral cortisone or hydro cortisone should be given There is no evidence that adrenocortical insufficiency following corticoid therapy ever becomes refractory to treatment with ACTH (Fredell et al 1955) A different condition which should not be confused with adrenal hypoplasia is resistance to ACTH which may develop after several months of treatment This is probably due to rapid destruction of the ACTH and it can be demonstrated by the failure of the ACTH to influence the eosinophil count and the 17 ketosteroid excretion The treatment should be changed to one of the corticosteroids

Local treatment with hydrocortisone has been adopted with varying degrees of success Truelove (1956) has used an ampoule of 250 milligrams of hydrocortisone (free alcohol) dissolved in 50 millilitre of 50 per cent ethyl alcohol which is emptied into a standard intravenous infusion bottle containing 500 millilitres of normal saline solution The hydrocortisone is sufficiently soluble to be held in this dilution and the diluted alcohol does not appear to irritate the colonic mucosa The water soluble hemisuccinate of hydrocortisone is now becoming available and is simpler to use The hydrocortisone is dripped into the rectum through a standard trans fusion set at a slow and steady rate so that there is no stimulus to ejection The amount of fluid is gradually increased from one quarter to one half a bottle each night immediately before the patient settles down to sleep and the treatment is continued for 2–3 weeks Local treatment appears to be most effective in early cases of ulcerative colitis and a remission may be induced more rapidly than by systemic therapy It is also the treatment of choice in proctosigmoiditis

Some numerical data will now be given to support the opinions which have been expressed In a review of a large series of patients with ulcerative colitis treated in Toronto Maltby et al (1956) have shown that there was no difference in mortality between the decades 1930–1940 and 1940–1950 despite the introduction of the sulphonamides and antibiotics However in the quinquennium 1950–1955 following the introduction of ACTH and the corticoids the mortality fell from 40 to 11 per cent In 109 patients treated with the hormones no serious com plication was observed except 1 case of adrenal insufficiency Of patients reaching

the stage of complete remission about 50 per cent unfortunately relapsed again within 2 years On the other hand the indications for surgery were broadened and many patients who would formerly have been too ill were now rendered fit for operation Elliott and Giansiracusa (1954) found that of 33 patients given short term hormone treatment 21 (63 7 per cent) went into remission but of these only 12 remained in remission at the end of 2 years

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cases 31 per cent of those treated with cortisone had remained free from symptoms as compared with 35 per cent of the controls The total deaths were now 8 per cent in the cortisone treated group and 16 per cent in the control group

In acute ulcerative colitis hormone therapy is the treatment of choice If a remission occurs it should be confirmed by sigmoidoscopy and radiography and treatment should not be completely suspended until the results of these have returned to normal Withdrawal of the hormones should be carefully supervised In fulminating cases hormone therapy should be used to avoid the necessity for emergency ileostomy and to make the patient fit for elective surgery should that prove desirable Where a remission occurs in acute idiopathic ulcerative colitis it should be seen if it will persist without therapy but if there are withdrawal symptoms or relapse a maintenance dose should be determined In chronic active colitis continuous treatment is usually necessary and the disease often persists even though there is a symptomatic remission Emotional difficulties may be the reason for failure to improve and the hormones are sometimes of value in making the patient accessible to psychotherapy

The effects of the long term control of chronic ulcerative colitis by continuous therapy are not yet known particularly the extent to which the disease may progress and lead to complications such as stricture and neoplasm despite symptomatic relief When there are gross structural changes in the bowel the hormones cannot be expected to reverse them In these cases the function of the hormones is to make the patient fit for surgery and paradoxically enough the effect of the introduction of hormone therapy in idiopathic ulcerative colitis up to the present has been to increase the proportion of patients undergoing radical surgical treatment of the disease In the future more attention will have to be paid to treating cases of ulcerative colitis with the hormones at the earliest possible stage in the disease Resolute treatment at this phase supplemented by attentive supervision might prevent the irremediable damage to the colon which is nowadays so often present

### *Regional ileitis*

Regional ileitis occurs with only about one tenth the frequency of ulcerative colitis and though there have been a number of reports of isolated cases treated with the hormones there have been no large series and no controlled trials The effects are somewhat similar to those in ulcerative colitis—diminution in fever and diarrhoea increase in appetite and well being—and in an occasional patient there is a striking remission but most observers have the impression that the hormones *have a smaller therapeutic effect in regional ileitis than in ulcerative colitis* (Van Patter et al 1954 Cooke 1955)

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# CHAPTER 3

# USES AND DANGERS OF ANTIBIOTICS

L P GARROD

ANTIBIOTICS may be administered orally either for the sake of an effect in the alimentary tract itself or because this is a convenient route of administration to achieve a systemic effect Although the object may be systemic incidental local effects are nevertheless commonly produced and these almost without exception are of an undesirable nature The worst of these result from a suppression of the normal flora of the bowel for which this paradoxical and unwelcome development has given us a new respect

## PHARMACOLOGY

Antibiotics are divisible into three classes according to their behaviour when administered orally Whether their effect is local or systemic or both depends mainly on their absorbability but to a lesser extent on other factors

### Streptomycin neomycin polymyxin, and bacitracin

These antibiotics although all capable of exerting a systemic effect when given parenterally have almost none when given orally since the amount absorbed is negligible They are also stable under all conditions met with in the alimentary tract and consequently maintain a high concentration until discharged in the faeces the flora of which they modify profoundly but selectively since none of them is in the true broad spectrum class Nystatin is also to be placed in this category

### Penicillin

Penicillin is the only major antibiotic of which oral administration has an exclusively systemic effect The greater part of a dose of the usual forms of penicillin is destroyed by gastric acid only phenoxymethyl penicillin (penicillin V) resists this action It seems that this is not the sole factor preventing complete absorption since only 25 per cent of an oral dose of penicillin V is excreted in the urine (Heatley 1956) in contrast to about 60 per cent so excreted when penicillin is given par enterally The fate of that part of a dose which traverses the stomach unaltered and is yet unabsorbed is not known for certain but any which reaches the lower part of the small intestine where a profuse and varied flora begins to appear is liable to destruction by penicillinase—an enzyme formed by various coliform bacilli In the lower bowel such destruction would be rapid hence penicillin given alone has no action here

### The tetracyclines

Chlortetracycline (aureomycin) oxytetracycline (terramycin) and tetracycline (achromycin Tetracyn) are the broad spectrum antibiotics *par excellence* and consequently exert a profound local effect as well as the systemic action for which

they are usually given They are not completely absorbed and the larger the dose the higher is the proportion of it which remains unabsorbed (Brainerd et al 1951 Herrell et al 1950) The concentration in the bowel is raised further by excretion in the bile This continuous process of biliary excretion followed by some re absorption is the reason why even the least stable of the series chlortetracycline persists in the blood for many hours after a single dose (Gray et al 1953) The same process apparently accounts for the very high concentrations maintained in the blood by novobiocin (Taylor et al 1956) although with this antibiotic the very low rate of renal excretion is an equally important factor

Emphasis on biliary excretion of the tetracyclines must not be thought to imply that other antibiotics do not behave similarly like many other drugs most anti biotics given parenterally are known to be excreted in the bile in concentrations higher than those present in the blood This is true of penicillin but it has no such effect since little re absorption follows On the other hand the stability of the tetracyclines in the intestinal contents enables them to traverse the whole length of the bowel and to appear in high concentration in the faeces sometimes with striking effects on their appearance and odour and never without a far reaching influence on their flora

**Chloramphenicol**

Chloramphenicol is in the same category but rarely causes so much local dis turbance evidently because its range of anti bacterial activity is narrower it has little action on clostridia and a weaker one than the tetracyclines on other Gram positive elements The more selective of the newer antibiotics erythromycin and novobiocin spare the Gram negative elements almost entirely and hence cause even less disturbance of the bowel flora They must nevertheless be placed in the category of antibiotics having a local as well as a systemic action—for two reasons (1) they are excreted in the faeces and must suppress the few faecal species sen sitive to them and (2) both have been used with striking success to eliminate staphylococci when these have proliferated unduly in the bowel

## THERAPY

Some idea of the results to be expected from treating acute intestinal infections with antibiotics can be gained by determining the sensitivity to them of the causal organisms Although there is much information about this data for different antibiotics are often not comparable because of differences in the method of test The Table gives the results of tests recently carried out by the author in order to provide comparable data for the purposes of this chapter

By far the most active of the seven antibiotics tested is polymyxin but this can safely be given only in small doses parenterally and attains correspondingly low concentrations in the blood and tissues It is hence chiefly of interest for its local action that is when given orally Next in activity—apart from neomycin which is also rarely given except by the oral route—are the tetracyclines Of these tetracycline and oxytetracycline have about four times the activity of chlor tetracycline against salmonellas and shigellas this difference may be due in part to the instability of chlortetracycline in an alkaline medium The performance of chloramphenicol may seem relatively unimpressive but this antibiotic attains

TABLE

SENSITIVITY OF SPECIES OF BACTERIUM SALMONELLA AND SHIGELLA TO 7 ANTIBIOTICS

| | *Minimum inhibitory concentrations (μg/ml)* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Chlor amphen icol* | *Chlor tetra cycline* | *Oxy tetra cycline* | *Tetra cycline* | *Strepto mycin* | *Neo mycin* | *Polymyxin* |
| *Bacterium coli* | 1 | 1 | 0 25 | 0 12 | 2 | 0 5 | 0 25 |
| 0 26 | 8 | 1 | 1 | 1 | 4 | 1 | 0 06 |
| 0 55 | 4 | 0 5 | 0 5 | 1 | 2 | 1 | 0 25 |
| 0111 | 8 | 1 | 1 | 1 | 4 | 2 | 0 25 |
| 0119 | 4 | 1 | 1 | 1 | 2 | 1 | 0 25 |
| 0127 | 4 | 0 5 | 1 | 0 5 | 16 | 1 | 0 25 |
| 0128 | 8 | 1 | 1 | 1 | 2 | 0 5 | 0 25 |
| *aerogenes* | 8 | 8 | 2 | 2 | 2 | 0 5 | 0 25 |
| *friedlanderi* | 1 | 1 | 0 5 | 0 5 | 1 | 0 5 | 0 12 |
| *Salmonella typhi (3 strains)* | 2 | 4 | 1 | 1 | 8–16 | 0 5 1 | 0 06–0 12 |
| *paratyphi A* | 4 | 8 | 2 | 1 | 8 | 0 25 | 0 25 |
| *B* | 2 | 4 | 1 | 0 5 | 4 | 0 5 | 0 25 |
| *typhi murium* | 2 | 4 | 1 | 1 | 4 | 1 | 0 25 |
| *enteritidis* | 4 | 4 | 1 | 1 | 16 | 1 | 0 5 |
| *thompson* | 4 | 4 | 1 | 1 | 8 | 2 | 0 5 |
| *Shigella sonnei (2 strains)* | 4–8 | 8 | 1 2 | 1–2 | 2–4 | 1 | 0 06–0 12 |
| *flexneri* 1 | 1 | 2 | 0 5 | 0 5 | 2 | 2 | 0 12 |
| 2 | 1 | 2 | 0 5 | 0 5 | 4 | 4 | 0 12 |
| 3 | 1 | 2 | 0 5 | 0 5 | 8 | 4 | 0 12 |
| 4 | 2 | 2 | 0 5 | 0 5 | 4 | 4 | 0 12 |

(Res lts of or g l a d h therto unp bl h d ob er at o s *M th d* l m ll l t e of doubl d d l t s of l t o of t b t dd d t 14 m ll l tre f m t t ct p pt g f pH 7 4 d pl t po red A rf oc l ted w th l m ll m t loopf l of l 500 d l t o of 4-ho b oth c lt re observ d f prese ce of growth vi bl to naked eye after 18 ho rs at 37 C )

higher concentrations in the blood dose for dose than the tetracyclines To account for its superiority for the treatment of enteric fever some additional factor must nevertheless be assumed this may be a greater capacity to penetrate foci of infection or individual cell membranes

Species of proteus and pseudomonas not included in these tests are variable in their sensitivity to most antibiotics but generally much more resistant to chlor amphenicol and the tetracyclines than the species studied Hence they sometimes assume predominance in the bowel when these antibiotics are being administered

**Typhoid fever**

That chloramphenicol has a specific action in typhoid fever was first shown by Woodward et al (1948) in Malaya It is now standard treatment for this disease and an extensive literature on this subject emanates largely from Latin countries in both hemispheres where opportunities for its study are numerous When adequate doses are given fever abates in 3–4 days and recovery follows although there is a substantial liability to relapse Haemorrhage or perforation still occur but the latter may not require surgical intervention The mortality is greatly reduced

A new complication occasionally seen in severe cases after 2–3 days treatment is vasomotor collapse with tachycardia prostration and falling temperature,

a condition which is ascribed to the liberation of endotoxin from typhoid bacilli which have been destroyed

Chemotherapy particularly at an early stage interferes with the normal bodily response to the infection as has been shown by studies of agglutinin formation Doubtless mainly for this reason and because the drug does not entirely eliminate the organism relapse is common and efforts have been made to devise a system of treatment which will prevent this interference The alternatives are a single pro longed course of chloramphenicol a shorter initial course followed by another at about the expected time of relapse and either of these accompanied by a series of daily injections of 0 1 millilitre of T A B vaccine to stimulate immunity The first of these policies is advocated by El Ramli (1953) who reported a relapse rate of only 3 9 per cent after a course of 12 5 milligrams per kilogram given twice a day and continued for 12 days after defervescence John and Vinayagam (1952) on the other hand had more relapses after a single course than after two In the experience of Marmion (1952) with 300 cases in Egypt the relapse rate was 18 per cent after giving 0 5 gramme 4 hourly and later 0 25 gramme 4 hourly for a total of 9–14 days but no less than 42 per cent when the same doses were given in 2 shorter courses with a 7 day interval When vaccine was also given these figures fell to 17 6 and 4 8 per cent why vaccine should have made so much difference in only one group is obscure Woodward et al (1952) described a case in which relapse followed no fewer than 60 days of continuous chloramphenicol treatment while doubtful whether the best system could yet be defined they were inclined to favour intermittent treatment perhaps reinforced with vaccine during the second course Marmion (1955) in a general account of more recent experience advises a daily dose of 50 milligrams per kilogram in 2–6 individual doses until the tempera ture falls followed by half this dose for a further 14 days a large initial loading dose which has sometimes been given is considered inadvisable

It is now quite clear that drugs of the tetracycline group are all much inferior to chloramphenicol for the treatment of typhoid fever On the other hand it has been suggested that one of them should be given with chloramphenicol or after it one reason being that they are excreted in much larger amounts than chloram phenicol in the bile

Another antibiotic to be considered is penicillin The typhoid bacillus is not as insensitive as most other intestinal Gram negative bacilli to penicillin and it was predicted by the Oxford workers in the early days of the study of this antibiotic that it might eventually prove useful in the treatment of salmonella infections McSweeney (1946) used it in combination with sulphathiazole obtaining favour able results which others could not confirm at least one case (Boger et al 1951) has since been successfully treated with very large doses of penicillin alone There is evidence so far not conclusive that this treatment may be successful for carriers Penicillin is bactericidal whereas chloramphenicol is merely bacteriostatic and consequently neither diminishes the liability to a persistent carrier state when used in the treatment of the disease nor affects that state once established

The favourable report of Benavides et al (1955) on the results of treating 15 cases of typhoid fever in children in Mexico City with synnematin B has a bearing on this since this substance is identical with cephalosporin N and the latter has been shown by workers at Oxford to be a form of penicillin (Florey 1955) It may yet prove that treatment with large doses of some form of penicillin although

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| *Salmonella typhi (3 strains)* | 2 | 4 | 1 | 1 | 8 16 | 0 5–1 | 0 06–0 12 |
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| *enteritidis* | 4 | 4 | 1 | 1 | 16 | 1 | 0 5 |
| *thompson* | 4 | 4 | 1 | 1 | 8 | 2 | 0 5 |
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| *flexneri* 1 | 1 | 2 | 0 5 | 0 5 | 2 | 2 | 0 12 |
| 2 | 1 | 2 | 0 5 | 0 5 | 4 | 4 | 0 12 |
| 3 | 1 | 2 | 0 5 | 0 5 | 8 | 4 | 0 12 |
| 4 | 2 | 2 | 0 5 | 0 5 | 4 | 4 | 0 12 |

(R lt of or g al d h th rto p bl h d observat o *M thod* l m ll l t of do bl d d l t ons f s l t f 1 b ot cs add d to 14 m ll l tre f m at e t act pept g of pH 7 4 d pl tes pou d Are o s rfac cul t d w th l m ll m t loopf l f l 500 d l t of 4-ho b oth cult obse ed fo pres ce of g wth s blet ked ey aft r 18 hours at 37 C )

higher concentrations in the blood dose for dose than the tetracyclines To account for its superiority for the treatment of enteric fever some additional factor must nevertheless be assumed this may be a greater capacity to penetrate foci of infection or individual cell membranes

Species of proteus and pseudomonas not included in these tests are variable in their sensitivity to most antibiotics but generally much more resistant to chlor amphenicol and the tetracyclines than the species studied Hence they sometimes assume predominance in the bowel when these antibiotics are being administered

**Typhoid fever**

That chloramphenicol has a specific action in typhoid fever was first shown by Woodward et al (1948) in Malaya It is now standard treatment for this disease and an extensive literature on this subject emanates largely from Latin countries in both hemispheres where opportunities for its study are numerous When adequate doses are given fever abates in 3–4 days and recovery follows although there is a substantial liability to relapse Haemorrhage or perforation still occur but the latter may not require surgical intervention The mortality is greatly reduced

A new complication occasionally seen in severe cases after 2–3 days treatment is vasomotor collapse with tachycardia prostration and falling temperature

oral polymyxin in a dose of 15–20 milligrams per kilogram daily for 10 days for eliminating the infection in chronic cases they were dealing with *S flexneri* in a home for mental defectives

**Amoebic dysentery**

Various antibiotics have some action on *Entamoeba histolytica* It is not always easy to distinguish a purely amoebicidal action from one exerted at least in part on bacteria with which the amoeba necessarily co exists not only in the body but in artificial culture Fumagillin is outstanding as a pure amoebicide active in a concentration as low as 1 in 4 000 000 and according to Anderson (1952) is highly effective in doses of only 10 milligrams daily in chronic amoebiasis The best antibiotic for acute amoebic dysentery appears unquestionably to be oxy tetracycline

Martin et al (1953) who treated 538 cases in Korea on various systems had only 6 relapses in 104 cases treated with oxytetracycline for 10 days orthodox treatment with emetine and other anti amoebic drugs resulted in a good initial response but a high relapse rate These authors believe that the best treatment will prove to be with oxytetracycline together with one of the regular amoebicides Results in a short series suggested that only 5 days treatment with oxytetracycline and chloroquine may suffice Chlortetracycline is distinctly and chloramphenicol much inferior to oxytetracycline for this purpose

**Infantile gastro-enteritis**

Infantile gastro enteritis is a disease of multiple and sometimes unknown aetiology and very variable severity When there is no certainty that different workers were dealing with the same disease it is of little value to compare their results and there has been some dispute about the usefulness of both streptomycin and chloramphenicol The result of an organized trial (Report 1953) embracing 1 168 cases in 10 centres was to suggest that sulphadiazine which in the early stages had been given to controls was more effective than either chloramphenicol or chlortetracycline When the condition is known to be due to one of the patho genic types of *Bacterium coli* it would seem from the findings in the Table (page 26) that any of several antibiotics might well have some beneficial effect on it but clinical results in cases of defined aetiology have yet to be reported

## PROPHYLAXIS

**Pre-operative preparation of the bowel**

The use of chemotherapeutic drugs as intestinal antiseptics has greatly facilitated colonic surgery mainly by minimizing the effects of peritoneal soiling but also by reducing gaseous distension For some years only the less soluble sulphonamides were available then streptomycin was given in addition sometimes for too long a period during which organisms became resistant to it

Chlortetracycline was then hailed as the most widely effective single drug—as indeed are all the tetracyclines—and was used for some time before its dangers became manifest Opinion now favours antibiotics having only a local action but choice and methods vary

To ensure success the bulk of the material in which the drugs must act should

more arduous for the patient is worth while because it more certainly eradicates the infection

**Other salmonella infections**

Paratyphoid fever responds to chloramphenicol like typhoid and is usually so treated Chloramphenicol is also indicated in the more severe cases of salmonella enteritis of the food poisoning type Clinical response is satisfactory but the organism frequently persists in the faeces (Ross et al 1950b) Penicillin has also been tried in the treatment of this infection with results at least equal to those obtained with chloramphenicol (Rabe 1955) Salmonella enteritis is an infection of very varying severity depending on which of many species causes it and on the age and general condition of the patient When caused for instance by *Salmonella typhimurium* in a healthy adult it is usually a comparatively mild and self limited disease of only 2–3 days duration and it is doubtful whether a potentially danger ous drug such as chloramphenicol need be given to such a patient An alternative is oral streptomycin which is harmless and probably more effective in eliminating the organism from the bowel

More severe infections in infants or debilitated elderly subjects those accom panied by septicaemia or producing a typhoid like state and those due to more virulent species such as *S choleraesuis* should of course be given the benefit of systemic chemotherapy

**Bacillary dysentery**

Sulphonamide treatment was formerly satisfactory for this disease but so many strains of dysentery bacilli are now resistant to these drugs that it has largely lost its usefulness Several antibiotics can replace them and it is difficult on present evidence to decide which is the best They have been judged by two criteria the clinical response and reduced mortality in severe cases and the rate of elimination of bacilli from the faeces in mild ones Garfinkel et al (1953) who treated 1 408 cases mostly of severe *Shigella flexneri* infection in prisoners of war in Korea commend chlortetracycline or oxytetracycline to which chloramphenicol was only slightly inferior they tried several dosage systems and obtained satisfactory results from a total of only 4 grammes given in 3 doses in 24 hours McFadzean and Stewart (1952) on the basis of experience with severe cases in Hong Kong recommend chloramphenicol There is conflicting evidence about the value of streptomycin owing perhaps to different methods of administration some have given it parenterally and others orally at intervals varying from 4 to 12 hours Chang and Su (1951) gave it by both routes to children in Shanghai obtaining a recovery rate of about 97 per cent (in patients treated with sulphonamide 86 per cent) Ross et al (1950a) used the oral route only giving 400 milligrams 4 hourly with good results both in alleviating the disease and in eliminating the bacilli Much the largest of several subsequent series of cases treated by oral streptomycin is that of Sangster (1956) who recommends 4 doses a day for 5 days this eliminated the organism in 86 per cent of patients and a second identical course cleared a further 11 5 per cent Murphy (1955) also judging the effect by the number of patients with a succession of negative stools after treatment obtained his best results in *S sonnei* infections by giving streptomycin and oxy tetracycline together orally Finally Lieberman and Jawetz (1951) recommend

because nutrients become available without competition Alternatively it may remove powerful restraining influences several species inhabiting the mouth and bowel are known to form antibiotics or other inimical substances themselves and these may be assumed to preserve a normal balance and to repel invasion by out siders Thirdly the antibiotic being administered may actually stimulate the growth of the resistant species causing the super infection There is no doubt of the reality of such stimulation (Garrod 1951) it is one of many examples of the Arndt Schulz law (*kleine Dosen rei en grosse Dosen lahmen*) but how far it operates in producing these infections cannot be said

Penicillin suppresses the normal flora only in the mouth and upper air passages and then only when fairly large doses are given leading to its appearance in sufficient concentration in the saliva and other secretions The effect of this may be a stomatitis or glossitis due to the proliferation of coliform bacilli or *Candida* (*Monilia*) More serious are the effects of antibiotics which largely suppress the flora of the bowel and among these the tetracyclines are pre eminent owing to their wide range of antibacterial activity and to the fact that they are not only incompletely absorbed but re excreted in the bile

A distinction should be drawn between two different gastro intestinal side-effects of these drugs They frequently cause nausea with or without mild diarrhoea presumably by acting merely as chemical irritants It is claimed for tetracycline apparently with good reason that it is less liable to produce these effects than chlortetracycline or oxytetracycline Secondly they predispose to super infections with resistant organisms one result of which may be a diarrhoea of far greater severity Their antibacterial actions are so nearly identical and cross resistance between them is so complete that any difference between them in this tendency would be inexplicable and it probably does not exist

**Types of organism causing super infections**

*Candida albicans* —A stomatitis in severer cases amounting to frank thrush and pruritus ani due to the proliferation of this or other yeast like fungi in the mouth and lower bowel respectively is fairly common after several days of treatment with one of the tetracyclines chloramphenicol can also have these effects Occasionally candida infection assumes a more extensive form invading the bronchi and even the blood stream recognition of this possibility came with the description of 3 fatal cases of generalized candida infection following antibiotic therapy by Brown et al (1953)

*Proteus and pseudomonas Proteus species and Ps pyocyanea* —These are more resistant to the tetracyclines and some other antibiotics than other coliforms and it has often been observed that antibiotic treatment directed at suppressing the bowel flora leads to their extensive proliferation This may have little untoward local effect apart from some diarrhoea but invasion of other parts of the body may be more dangerous (Karakasevic 1955 Yow 1952)

*Staphylococcus pyogenes* —Attention was first drawn to the occurrence of a staphylococcal dysentery during treatment with oxytetracycline by Jackson et al (1951) Since then similar cases many of them fatal have been reported from Switzerland (Bernhart 1952 Meier 1952) from England (Gardiner 1953) from Scotland (Hay and McKenzie 1954) from Germany (Gsell and Kesselring 1955) and elsewhere That oxytetracycline is not alone to blame for this is proved

be reduced a consideration demanding a low residue diet and saline cathartics The treatment chosen should produce the desired effect within 2 days It should preferably employ an antibiotic which is not absorbed is unlikely to be required later for systemic use and to which resistance is not readily acquired These conditions are all fulfilled by neomycin introduced for this purpose by Poth et al (1950) and now widely used often in combination with a sulphonamide

A method which has been found satisfactory at St Bartholomew s Hospital London is to administer 2 grammes of phthalyl sulphathiazole 6 hourly and 1 gramme of neomycin 12 hourly for 2 days before operation the first dose of each being double this quantity

Another combination for which merit has been claimed is neomycin with erythromycin or carbomycin for the sake of the action of the latter drugs on enterococci Four doses of this combination in one day are said to suffice (Prigot et al 1954–5a and b) Perhaps the most complete suppression of the intestinal flora can be achieved by administering neomycin polymyxin and bacitracin together (Jawetz and Bierman 1952) Such treatment is very costly its necessity is doubtful and there may well be some risk of replacement with undesirable species

**Other prophylactic uses**

It is strongly believed in some quarters that surgical use of antibiotics is grossly excessive Most of the supposed indications for their pre operative administration—including the fear of litigation should this precaution have been omitted when things go wrong—are outside the scope of this chapter but a policy for gastrectomy and other operations on the stomach comes within it The bacteria involved here are those of the mouth and these are in general penicillin sensitive If any anti biotic is given prophylactically it should therefore be penicillin only the necessity for even this is doubtful In 443 gastrectomies (Hasslinger 1956) there were fewer post operative infections of the wound or air passages in 290 patients given no chemotherapy than in 153 who were given penicillin Similar findings are reported by McKittrick and Wheelock (1954)

Whatever else may be thought advisable patients about to undergo an operation on the stomach or intestinal tract should not be given penicillin with streptomycin or any of the tetracyclines nor should these be given post operatively unless for a very good reason These forms of medication are the almost invariable precursors of acute staphylococcal enterocolitis This condition is described in the following section where an explanation is suggested for the peculiar liability to it of this class of patient

## SUPER INFECTIONS COMPLICATING ANTIBIOTIC THERAPY

Soon after penicillin came into general use it was recognized that otherwise successful treatment may be complicated by the supervention of a fresh infection due to another and resistant organism either at the site of the disease or elsewhere The reasons for this are not yet entirely understood but there are at least three possibilities of which any or all may operate Super infections usually occur in parts of the body possessing a varied normal flora which the antibiotic suppresses and this may be said to create a bacterial vacuum which tends to be filled if only

because nutrients become available without competition Alternatively it may remove powerful restraining influences several species inhabiting the mouth and bowel are known to form antibiotics or other inimical substances themselves and these may be assumed to preserve a normal balance and to repel invasion by out siders Thirdly the antibiotic being administered may actually stimulate the growth of the resistant species causing the super infection There is no doubt of the reality of such stimulation (Garrod 1951) it is one of many examples of the Arndt Schulz law (*kleine Dosen rei en grosse Dosen lahmen*) but how far it operates in producing these infections cannot be said

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by the fact that Gsell and Kesselring s 5 patients all of whom died had been given tetracycline It is most important to recognize that this extremely dangerous condition—and this applies equally to candida infections—can also be caused by combined treatment with penicillin and streptomycin Fairlie and Kendall (1953) describe 3 such cases Fowler (1955) 3 and Sanders and Kinnaird (1955) another while several other reports describe cases in which this combination was used although the authors attribute the complication to a few doses of a tetracycline *given subsequently No explanation has been given for the action of this combina* tion in the bowel when administered parenterally The action of its two constit uents adds up to that of a broad spectrum antibiotic they must reach the intestine in the bile and perhaps the intestinal secretions and presumably the suppression of coliform bacilli by streptomycin protects the penicillin against destruction by penicillinase

The staphylococcus causing this condition is usually resistant to penicillin streptomycin and the tetracyclines and—in Great Britain at least—sensitive to chloramphenicol and erythromycin The suggestion has been made that the infec tion can be autogenous the staphylococcus in a nasal carrier acquiring resistance during treatment This is highly improbable and cross infection from another source must be regarded as the usual mode of infection It is now well recognized that antibiotic resistant staphylococci their pattern of resistance depending on what antibiotics are being used can become widely distributed in hospitals caus ing many minor as well as a few major infections many of the staff carry them in their noses and they can be recovered from bedding dust and even the air of a ward

The type of patient commonly attacked is elderly and debilitated both by the primary disease and by the effects of a major operation though this is not always the case One of Hay and McKenzie s fatalities was in a previously healthy child being treated merely for an intestinal carrier condition but the risk is evidently much greater in surgical cases particularly after abdominal operations when a tetracycline has been used for pre operative preparation of the bowel It seems very probable although this appears not to have been suggested before that starvation is a factor in surgical cases Gastrectomy involves withholding food by the mouth for 36–48 hours and other operations for a lesser period the bowel of such a patient must be empty Antibiotics in its lumen thus attain a high concentration and remaining bacteria are unprotected from their action by food residues In no other circumstances could elimination of the normal flora be more complete

The diarrhoea is of rapid onset with profuse watery stools numbering as many as 20 daily containing mucosal sloughs and enormous numbers of staphylococci of which they yield an almost pure growth Dehydration is rapid and circulatory *collapse follows death often resulting within 2 days of the onset* The condition found at autopsy is an acute inflammation involving mainly the small intestine with superficial necrosis of extensive areas of the mucosa and an almost entire replacement of the normal flora by staphylococci The histological appearances produced are illustrated in Figs 11 and 12 The relationship if any between this and a form of prostrating post operative diarrhoea which used sometimes to be seen before antibiotics came into use is not *known Similar cases still occur in which* no microbic cause is identifiable



FIG 11 —Transverse section of part of jejunum from a fatal case of acute staphylococcal enterocolitis

Male aged 51 years given penicillin and streptomycin prophylactically after partial gastrectomy onset of profuse watery diarrhoea 2 days later death occurred on the following day despite intravenous fluids erythromycin and so on At autopsy there were areas of superficial necrosis of the mucosa throughout the small intestine most extensive about the middle of the jejunum The darkly stained material on the denuded surface consists entirely of masses of staphylococci (Gram stain × 50)

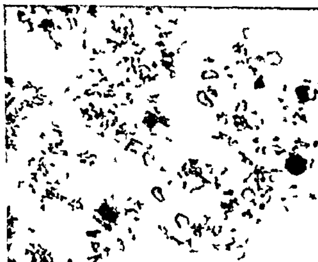


FIG 12 —High power view of an area from Fig 11 in which the bacteria are less densely packed showing that these are all Gram positive cocci (Gram stain × 1 000)

**Prevention and treatment**

The overgrowth of candida during antibiotic treatment can be prevented by also administering nystatin in doses of 500 000 units 3 times a day the same treatment is applicable to the established infection This is a purely anti fungal antibiotic of very low solubility and probably has little action outside the alimentary tract

The prevention of staphylococcal super infection is both more important and more difficult The first line of defence is to shield the patient against exposure to cross infection with antibiotic resistant staphylococci but we do not yet know how to control the multiplication and migration of these organisms What we do know is that their pattern of resistance is determined by local therapeutic practice every hospital or clinical unit makes its staphylococci what they are Hence a general restriction of the use of antibiotics particularly for prophylactic purposes of doubtful necessity is strongly to be commended The use of the tetracyclines or of penicillin with streptomycin as prophylactics in connexion with operations is equally strongly to be condemned Preparation for operations on the colon is best achieved with sulphonamides and neomycin as described in an earlier section If tetracyclines are given for other indications moderate doses (1 0–1 5 grammes daily) are safer than large ones

The stools of any patient at risk who develops diarrhoea should be examined at once by direct microscopy An undue proliferation of staphylococci can readily be detected in a simple stained film and administration of the antibiotic responsible can be stopped forthwith If this is done in time the outlook is better than published descriptions suggest I have seen only one fatality among at least 30 patients in whom a staphylococcal enteritis occurred although it cannot be known whether all of these would have developed the full picture of profuse diarrhoea and collapse had the nature of the condition not been recognized so early

In fully developed cases the other necessary measures are fluid replacement and the administration of an antibiotic to which the staphylococcus is sensitive intravenous administration may be advisable at first Erythromycin has generally been used and novobiocin has also been found effective It is a sound policy to reserve these antibiotics in hospital practice if not solely for such imperative indications as this at least for such purposes that the development of resistance to them in staphylococci will not be promoted Yoghourt has been administered for both the prevention and the treatment of staphylococcal enterocolitis with the idea of substituting a harmless for a potentially dangerous intestinal flora This procedure innocently ignores the fact that *Lactobacillus acidophilus* is highly sensitive to the tetracyclines and to erythromycin and hence could not be expected to establish itself in the usual circumstances of either preventive or curative use The development of strains of lactobacilli resistant to these antibiotics would remove this objection and this possibility is now being explored

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## CHAPTER 4

# COLLAGEN DISEASES AND THE GASTRO INTESTINAL TRACT

W A BOURNE

## INTRODUCTION

THE collagen diseases comprise a group of syndromes of whose nature we are ignorant but whose manifestations are located largely in connective tissue (Bywaters 1956) Among these manifestations the most important are fibrinoid necrosis vascular lesions raised *gamma* globulin serositis arthritis and lymph adenopathy with the occasional addition of changes in the kidneys blood skin and other tissues and organs Damage to tissues and organs in these clinically vague diseases is definite but usually non specific It is secondary to the alterations in the collagen ground substance fibroblasts elastic fibres and reticulum of connective tissue It is associated with infiltration by or changes in leucocytes or leucocyte activity on which diagnosis sometimes depends

To these syndromes the gastro intestinal tract rarely adds symptoms or signs which have clinical or pathological significance In very few collagen diseases does it suffer characteristic secondary changes due to the manifestations in connective tissue which the injuries of the disease process produce

The conception of a group of diseases associated with injury to connective tissue widely distributed as it is throughout the body was regarded by its introducers (Klemperer et al 1941) as a still further extension of the thesis of Morgagni that diseases reside in certain organs and the later realization that they might reside in certain organ systems such as that responsible for haemopoiesis Such a conception is not at first sight likely to have much relevance for the digestive system in which organs and organ systems are particularly prominent In fact the development of our present views is closely related at two points with the digestive system The new conception led to a re assessment of the observations of Osler (1903) who reported cases in which marked disturbances of the digestive tract were associated with skin and joint lesions sometimes before the appearance of the latter Osler s work was remarkable for its almost purely clinical nature and the relatively simple and often dramatic nature of the gastro intestinal symptoms he observed gave clear-cut data to correlate with those obtained from observation of the skin and joints

Another point of contact was made when it appeared that rheumatoid arthritis might be included among the collagen diseases and that rheumatoid pain and stiffness might be ameliorated by jaundice as well as by other conditions It was this observation which suggested to Hench (1949) the potentially reversible nature of the rheumatoid process and was partly responsible for the trial of adrenal hormones in its treatment Although the value of jaundice as a therapeutic agent in rheumatoid arthritis has been criticized (Hartfall 1944) it is still believed that the failure of a damaged liver to render adrenal hormones inactive may play a part

in the therapeutic effect of jaundice in some cases (Sherlock 1955) or that some hepatic detoxicating action may account for the failure of orally administered hormones which must run the gauntlet of a healthy liver though parenteral treatment is effective

The criterion applied by Klemperer et al (1941) for the diagnosis of damage to collagen was the appearance of fibrinoid change in connective tissue As this abnormal material and others (haematoxylinophilic bodies or abnormal sclero protein) accumulate or cellular necrosis in vessel walls is followed by ischaemia undoubted changes occur in the quantity and quality of body fluids These are not due to digestive disturbances (Robb Smith 1952) but are secondary to this accumulation of abnormal materials which disturbs the vital layer of connective tissue through which all extracellular metabolic processes must be mediated Abnormal transpeptidization catalysed by proteolytic enzymes may be the mechanism responsible for such damage The essential mechanisms of the gastro intestinal system are however intracellular depend on other types of enzyme action and tend to be mediated at cell surfaces There is an essential difference in this respect which implies that in collagen disease disturbances of the gastro intestinal tract are not due to changes in essential activity of its cells but are secondary to changes in body fluids or blood supply Collagen disease may interfere with the supply of the raw materials of cell metabolism but leaves essential gastro intestinal intracellular processes untouched

In considering such a difference it is worth recalling that collagen diseases are commonly described as disorders of the mesenchyme In the embryo the mesoderm grows rapidly and does not remain long undifferentiated but splits into the somatic mesoderm and the splanchnic mesoderm enclosing the coelomic cavity The splanchnic mesoderm becomes closely associated with the entoderm so that the primitive gut very early acquires two layers one to give rise to the epithelial and mucosal lining of the gut tract and its glands and the other—the mesoderm—to give rise to the muscular and connective tissue layers of the gut wall It is these latter layers to which in the abdomen the peritoneum is added which will be susceptible to mesenchymal disease Striated muscle related to the digestive tract (the pharyngeal constrictors the diaphragm and the pelvic floor) will likewise be liable to attack Finally the blood supply to the whole body arises in irregular masses of mesenchymal cells lying between the splanchnic mesoderm and the entoderm so that the vessels of the gastro intestinal tract are susceptible in collagen disease Any disorder of the mesenchyme will clearly involve structural or circulatory changes in very intimate connexion indeed with the essential tissues of the digestive organs

Finally mention should be made of the part occupied by the gastro intestinal tract in the aetiology of these diseases Their cause is still unknown Hyper sensitivity to infecting organisms foreign proteins or drugs has been considered important The concept of stress syndromes has been elaborated and emotional physical infective or biochemical stress may at times appear to be related These forms of stress are very common and widely spread however and it does not seem possible to relate them confidently to diseases of insidious and often febrile onset liable in any case to be complicated by lowered resistance to infection Ulcerative colitis parasitic infestation and new growth excepted primary dis orders of the digestive tract have not been thought to play a significant part nor

do suspect infecting agents notably streptococci commonly invade it Sulphon amide treatment has been recorded as preceding the development of collagen disease but in almost all the recorded cases this has been given for a respiratory infection As Rose (1956) pointed out cases should occur equally with infections in other sites if sulphonamide hypersensitivity were responsible and disorders of the intestine frequently call for such therapy It does not appear that in the aetio logy of collagen disease disorders of the alimentary system will with rare exceptions need special consideration

Against this general background the individual manifestations of gastro intestinal lesions in collagen disease will be reviewed The term usually includes *rheumatoid arthritis and ankylosing spondylitis polyarteritis nodosa generalized* lupus erythematosus dermatomyositis scleroderma rheumatic fever glomerulo nephritis Henoch Schonlein purpura erythema nodosum and others (Bywaters 1956) to which has been added thrombotic thrombocytopenic purpura

## GENERALIZED LUPUS ERYTHEMATOSUS

### Clinical Manifestations

Generalized lupus erythematosus affects particularly female patients although chronic discoid disease shows little sex difference It is recognized that visceral lesions may be present without skin lesions or that the latter may be confused with seborrhoea eczema rosacea psoriasis purpura or scleroderma or that typical erythema nodosum may occur The polymorphic nature of these mani festations has lent additional weight to Osler s description of gastro intestinal complaints as important Most later reports agree in the frequency of such symp toms in spite of minor post mortem evidence

Mucosal lesions are less common than skin lesions and tend to occur only at the height of the disease whereas the latter are usually present in latent periods (Tumulty 1954) If ulcerative they tend to heal Changes may involve the lip margins cheek tongue palate or pharynx be indistinguishable from the lesions of lichen planus or present as erythematous or petechial patches or as herpetic ulcers (Harvey et al 1954) They may be associated as in a case seen personally with lesions of the recto anal region so that simulation of the Stevens Johnson syndrome is very close Klemperer et al (1941) reported a similar case

The oesophagus is involved in 7 per cent of cases (Tumulty 1954) and severe dysphagia may be present due to lesions of its wall or from mediastinitis Though nausea and vomiting have been recognized as symptoms since Osler reported them gastric lesions are not frequent but ulceration secondary to arterial lesions and in one case a filling defect by radiological examination which proved on gastroscopy to be due to an oedematous haemorrhagic and eroded area (Golding and Gowing 1953) have been reported Bowel symptoms are commoner diarrhoea associated with vomiting colicky pain and tenderness being present in approxi mately 30 per cent of reported cases reviewed by Harvey et al (1954) Intestinal bleeding accompanies these symptoms usually mild but occasionally severe Sigmoidoscopic appearances closely resembling ulcerative colitis may be seen Peritonitis is frequently found at autopsy but rarely causes symptoms nor do pancreatic lesions The spleen is frequently enlarged and the liver more often still though jaundice is rare

These numerous symptoms and signs are rarely the first features of the disease though they are found in 20–25 per cent of patients Of 62 cases reported by Dubois (1953) they presented first in 6 and were prominent in 25 He considered the disease relatively common (half as frequent as rheumatic fever) and its protracted course—estimated by Tumulty to average 7 years—and its protean nature may obscure the disturbances of the alimentary tract

**Pathology**

In the diagnosis of generalized lupus erythematosus pathological investigations are of great importance The appearance of the characteristic cells is dependent on a factor associated with plasma *gamma* globulin which is responsible for degradation of polymorph nuclei and the resulting production of chemotaxis and phagocytosis There is hyperglobulinaemia which has been regarded as a fundamental anomaly (Golding and Gowing 1953) associated often with a depression of serum albumin *so that the thymol turbidity and cephalin cholesterol tests become positive* *Such* changes are found in many chronic diseases and should not be regarded as evidence of parenchymatous liver dysfunction especially since the serum bilirubin and alkaline phosphatase levels and bromsulphthalein test are normal (Sherlock 1955) A false positive serological test for syphilis present in 15–35 per cent of cases is an allied finding

When gastro intestinal haemorrhage is present or acute abdominal symptoms develop haematological findings become important Anaemia is a common feature and if haemolytic should suggest the diagnosis It is usually normocytic and normo chromic though hypochromia may be present and its characteristics will depend on the relative degrees of blood loss renal failure and haemolysis Leucopenia below 5 000 cells per cubic millimetre is usual and even in the presence of infection the total white count may not exceed 10 000

Gross post mortem changes characteristic of the disease are few and none appear in the stomach or bowel the diagnostic macroscopic findings being in the skin and endocardium Even microscopically collation of scattered findings in connective tissue blood vessels and blood kidneys and skin is likely to be necessary to sustain the diagno sis Fibrinoid degeneration of collagen needs interpretation against this general back ground It is for example well known that such degeneration is found in the base of a peptic ulcer

One visceral change—peri arterial fibrosis of the spleen—is found commonly enough to be regarded as characteristic though even this is not pathognomonic It consists essentially of an aggregation of concentric rings of stout collagen fibres with a few fibroblasts in an onion peel arrangement Peri splenitis tends to be present but is not peculiar to the disease nor is the peri hepatitis originally emphasized by Klemperer et al (1941) though capillarized and fibrous thickenings infiltrated by large and small round cells may show occasional fibrinoid change (Golding and Gowing 1953) Peritoneal adhesions of this type are frequent in some series and may be part of the polyserositis which is a feature of some cases though clinical manifestations due to them do not occur The liver may show focal necrosis secondary to vascular lesions or fatty infiltration such as is found in a number of generalized diseases Occasionally localized infective processes such as pylephlebitis or abscess formation are present

**Diagnosis**

Disorders of the alimentary tract are not often a primary presentation of generalized lupus and difficulties in diagnosis might not seem likely to arise This conclusion has however been based on reports of acute or subacute cases coming

to autopsy which are perhaps not characteristic The now recognized lengthy duration of the disease perhaps as long as an average of 7 years with repeated remissions of a year or more in as many as 12 patients out of 34 treated symptom atically (Tumulty 1954) will give lengthy periods in which assessment of symp toms is very difficult If an exacerbation involves the alimentary tract the association of abdominal pain and vomiting perhaps with melaena may simulate acute abdominal disease and as Golding and Gowing (1953) remark when these patients come under surgical jurisdiction it may be with difficulty that the surgeon s hand is stayed Loss of weight malaise anorexia and similar vague complaints frequently precede the relapse and confuse the picture If chronic discoid lupus is present the diagnosis may be at once suggested If there is doubt inquiry into the past history for a wide range of complaints—pleurisy and effusion rheumatoid arthritis nephritis pericarditis drug sensitivity haemolytic anaemia purpura or epilepsy—may lead to the tentative diagnosis and be supported by appropriate pathological investigations

### Prognosis

Increasing realization of the disease has not improved the ultimate prognosis despite the recognition of its subacute and chronic forms In these spontaneous remissions are frequent following involvement of the skin joints or pleura but much less common when other systems including the gastro intestinal are impli cated Gastro intestinal haemorrhage or necrosis of the intestinal wall may be responsible for a fatal termination and are attributable to vascular disease

### Treatment

There appears to be no cure for generalized lupus erythematosus the essential metabolic defect not being susceptible to any treatment Suppression of presumed side effects may however be achieved in many cases by ACTH or steroid therapy With these gastro intestinal symptoms respond well as a rule nausea vomiting pain and tenderness being relieved in a large proportion of cases Increase in appetite and ability to tolerate food produce a gain in weight and marked general improvement It does not appear however that the course of the disease is altered and the inherent but unexplained inability of these patients to combat infections remains Such infections must constantly be sought for and the suppressive effect of steroid therapy will introduce additional dangers if given unnecessarily A case has been reported (Harvey et al 1954) of a patient who died with peritonitis while receiving ACTH and had little evidence of the primary disease at autopsy Such dangers and other effects of steroid therapy on the alimentary tract make constant vigilance necessary

## POLYARTERITIS NODOSA

Polyarteritis nodosa is a pan arteritis in which fibrinoid degeneration attacks all coats of the smaller muscular arteries and arterioles It differs from generalized lupus erythematosus in the practical restriction of lesions to the vascular tree and in the predominance of males among those affected There is what has been termed a melange of diseases going by this name (Kranes 1956) which has been from time to time divided and re divided on the grounds of clinical findings distribution of lesions and morphological features Certain cases overlap with generalized

lupus and L E cells have been reported in them some have been classified as hypersensitivity angiitis with acute necrotizing inflammation around small vessels involving the liver and spleen but rarely the intestine others are classed with rheumatic arteritis in which the heart and lungs are mainly affected others appear to overlap with the so-called allergic granulomatous arteritis others have been related to temporal arteritis There is also the necrotizing arteritis found in hypertension It is however possible to attempt to distinguish one particular group of cases by clinical and histological criteria and in view of the benefits which treatment occasionally gives it is worth while to do so

**Clinical manifestations**

Symptoms related to the digestive tract occur against the background of a chronic indefinite illness Loss of weight malaise anorexia generalized weakness and pains and low fever are common so that general infections such as acute rheumatic fever typhoid fever or brucellosis may be suspected Diarrhoea vomiting or constipation are frequent and abdominal pain with diffuse tenderness may be due to lesions in the abdominal wall which is involved in at least 50 per cent of the cases (Miller and Daley 1946) In addition intra abdominal symptoms suggesting such conditions as cholecystitis peritonitis peptic ulceration appendicitis or mesenteric thrombosis were present in practically 50 per cent of a series of 230 cases reviewed by Mowrey and Lundberg (1954)

Clinical examination rarely shows the subcutaneous swellings thought formerly to be frequent Hepatomegaly with tenderness has been reported in 21 per cent of cases but splenomegaly is rare Pain and tenderness are usually referred to the epigastrium or right upper quadrant but the signs may be those of perforation or obstruction of a hollow viscus local inflammation or haemorrhage from the upper or lower digestive tract It does not seem that lesions of the buccal mucosa or upper orifices generally are found and they certainly have not the frequency of those seen in disseminated lupus The rectum and anus may however show changes Felsen (1941) described a case in which horizontal linear dark red streaks in parallel lines were seen on sigmoidoscopy and localized by a special technique to the vascular layer He described two other cases in which linear and nodular lesions often separated by skip areas were apparent It does not seem that the diagnosis of polyarteritis by this method has been recently reported though as in the case of generalized lupus non specific ulcerative colitis has been found to be associated

**Pathology**

The cause of these varied symptoms is a segmental necrosis of the media of the medium and small-calibre arteries accompanied by generalized oedema and progressing to fibrinoid necrosis Infiltration by inflammatory cells follows possibly with thrombosis infarction or aneurysm formation and finally fibrosis healing and possible re-canalization These changes occur in the vessels of *all* organs and tissues to a varying degree the liver coming third in order of frequency followed by the gastro-intestinal tract pancreas and mesenteric arteries and preceded only by the heart and lungs There is evidence that these areas of necrosis and oedema involving part or all of the wall of the muscular arteries occur more frequently at arterial bifurcations and branchings and this may account for their frequency at mesenteric attachments and their widely recognized tendency to involve the gastro intestinal tract So common is this that careful study of intestinal histology has been recommended in cases in which

focal embolic nephritis type I nephritis or malignant nephrosclerosis is suspected from the renal histological picture as a necessary measure to exclude polyarteritis (Davson et al 1948) Absence of gastro intestinal symptoms is no contra indication though uncommon The usual vascular lesions may be followed by erosion or ulceration of the mucosa leading occasionally to perforation and peritonitis or serous peritonitis with adhesions as in generalized lupus may be present

Arterial lesions have been found in the pancreas in 50 per cent of cases in the gastro intestinal tract in 42 per cent the spleen 37 per cent the gall bladder 16 per cent but infarction occurred in only 16 per cent of cases in the spleen in the liver 15 per cent and in the gastro intestinal tract and pancreas 6 per cent each The liver may also show interstitial hepatitis disruption of periportal tissues bile duct proliferation and parenchymatous degeneration Disturbance of liver function is however rare in spite of frequent clinical hepatomegaly and tenderness

A sub variety of polyarteritis different from periarteritis nodosa in every respect except the morphologic picture was described by Plaut (1951) who found arteritis of the appendix in 88 of 6 576 appendicectomy specimens an incidence of 1 34 per cent No clinical correlation could be established and there was no recurrence after operation A similar reversible inflammation involving the appendix and gall bladder appears to have been suggested by Kline and Young (1934) and the histological differentiation again needs to be made in conjunction with clinical findings

## Diagnosis

Miller and Daley (1946) specified as one of their clinical pictures of polyarteritis nodosa an atypical subacute or chronic abdominal illness The diagnosis should also be remembered in unexplained mesenteric thrombosis or retroperitoneal haemorrhage or when atypical lesions are found at laparotomy on patients with *brief histories suspected of intestinal obstruction acute appendicitis* penetrating or bleeding ulcers or malignant disease Frequent clues are found in a past history of peripheral neuritis sore throat arthralgias fugitive erythema and urticaria or asthma A second pointer is *the addition to the originally presenting* abdominal complaint of an unreasonable multiplicity of pathological lesions These findings in a middle aged male should arouse suspicion but confirmation can only be by biopsy and it is common to miss areas of skin and muscle involved while liver or renal biopsy gives non specific changes Early diagnosis is at present rarely achiev able and will probably not be until a laboratory test is evolved as reliable as the lupus erythematosus cell test in the disseminated form of that disease In abdominal conditions particularly other forms of arteritis may give difficulty in diagnosis From the Medical Research Council series of cases hypersensitivity to respiratory infections especially to those due to streptococci appeared to be the most likely cause in many (Rose 1956)

## Prognosis

The prognosis is in general bad but is not markedly affected by the abdominal condition *death usually occurring from damage to the central nervous system* the cardiovascular or renal systems The most favourable outlook is indeed in the localized arteritis of appendix or gall bladder

## Treatment

Steroid or corticotrophic therapy is probably most commonly used with a preference for oral administration Its value is still undecided but gastro intestinal

lesions are probably benefited although visceral infarctions have been attributed to it

## DERMATOMYOSITIS

It has already been pointed out that on general principles and from clinical observation sharp differentiation of collagen diseases is often difficult and dermatomyositis is a clear example Cutaneous lesions with extensive muscle weakness and tenderness are its essential clinical features but it may be acute with involvement of viscera or chronic with relative freedom from visceral damage Its full range is uncertain since skin changes are differently interpreted by dermatologists The relation of these skin lesions to calcinosis and the subcutaneous tissue lesions classified by Parkes Weber (1948) into symptomatic sclerodermas and specific disease sclerodermia or the systemic sclerosis of Goetz (1945) is still undefined

A review of the disease based on past case reports and reviews is for this reason unsatisfactory and an estimate of the extent to which the alimentary tract is involved is correspondingly unreliable The point at issue is very largely to determine the degree of damage done to the vital striated musculature of the pharynx larynx and diaphragm Early reports—for example of a child aged 6 years with raw buccal and pharyngeal mucosa ulceration of the intestine and oedema and round cell infiltration between the fibres of the muscular wall of the intestine or of another patient with widespread alimentary ulceration and disintegration of the muscle wall of the oesophagus—may not refer to the same disease since the criteria now applied to acute collagen diseases had not then been developed Similarly the uncertain mutual relationship of dermatomyositis and progressive scleroderma make reports of more chron c cases equally uncertain There are nevertheless cases which can now be regarded as forming a reasonably defined group and in which involvement of the alimentary tract can be studied

Another aspect which has lately attracted attention is the aetiological relationship of neoplasm to dermatomyositis New growths may be complicated by dermatomyositis in somewhat the same unknown manner as by thrombophlebitis migrans acanthosis nigricans polyneuritis or haemolytic anaemia A number of examples of this association have been reported where malignant disease of the alimentary tract was present

**Clinical manifestations**

Children and (in most reported series) females are mainly affected In the acute stage oedema of the face and patchy erythema with pain and weakness of proximal muscle masses are the main complaints These may be preceded or accompanied by fever joint pains or deformities and occasional evidence of cardiac lesions so that rheumatic fever or rheumatoid arthritis may be suspected at the outset If the disease continues to the chronic stage joint deformity and cutaneous atrophy—poikilodermia—may appear

Among the skeletal muscles involved in the inflammation and destruction produced by the disease are those of the palate and pharynx If these are involved early in a patient with fever an upper respiratory infection may easily be diagnosed and an infective basis postulated for the later manifestations If in addition sulphonamides or antibiotics are given diagnosis is further complicated More frequently however the pharyngeal muscles are involved only after the main

muscle masses elsewhere have shown marked weakness and after the appearance of oedema and erythema

The disturbance in deglutition produced by pharyngeal involvement produces some of the most outstanding features of the disease second only in importance to the impairment of respiration Regurgitation through the nose may be an early manifestation (in 7 of 25 cases reported by Sheard 1951) and is frequent at a later stage Epigastric distress perhaps from damage to the diaphragm may be associated

Associated with these disorders of function there are mucosal lesions O Leary and Waisman (1940) reported stomatitis in 9 out of 40 patients of whom 27 had dysphagia Wainger and Lever (1949) reporting the post mortem findings in 3 patients with emphasis on organs other than the skin and skeletal muscles found ulceration of the oesophagus jejunum ileum and rectum and oedematous brawny thickening of the intestinal wall in 1 case in whom during life there had been gross abnormalities radiologically Microscopically there were severe vascular lesions and it was considered that some of the histological findings closely resembled those found in systemic lupus erythematosus or diffuse scleroderma The difficulty of placing these cases into one diagnostic group is evident Since the introduction of steroid therapy the liability to ulcerative lesions may be increased partly from the increased liability to peptic ulceration and partly from diminished resistance to infection A case has been reported in which there were multiple perforated oesophageal gastric and duodenal ulcers after cortisone had been given Dysphagia may however be due to oesophageal disturbance indistinguishable radiologically from that found in scleroderma (Talbott and Ferrandis 1956)

It has recently been estimated (Curtis et al 1952) on the basis of a series of 45 cases that 18 per cent of patients with dermatomyositis have malignant tumours As the majority of patients are females in whom neoplasms of the sex organs are frequent the digestive tract is not often the site and in only 1 case in the above series was it involved Other reports have recorded the parotid gland oesophagus stomach gall bladder colon and rectum as sites of associated tumours usually in males The symptoms of dermatomyositis precede those of the tumour

### Pathology

At autopsy gross changes are not conspicuous Irregular areas of oedema or hyperaemia of the skin are present with occasional desquamation excoriation or vesicle formation The muscles appear pale and the long standing areas fibrotic Striated muscle which particularly concerns the digestive tract shows diffuse and focal inflammation with interstitial oedema and infiltration by lymphocytes Fibres swell and become hyalinized with loss of striation the sheaths proliferate and fibrosis finally occurs The walls of arteries and veins become thick and hyaline and as in polyarteritis ulcers in oesophageal epithelium or the gastric and intestinal mucosa may occur from ischaemia The liver and spleen may be affected in the same way or perilobular cellular infiltration be demonstrated

### Diagnosis

Digestive disturbances usually occur late in the disease after generalized muscular weakness and skin lesions have led to the diagnosis In rare cases buccal or rectal ulceration has presented first or severe dysphagia has been a very early symptom

The Stevens Johnson syndrome may be an alternative diagnosis and generalized lupus erythematosus needs exclusion by the absence of the typical pathological findings of that disease No characteristic and diagnostic features are present in biochemical investigations Serum *gamma* globulin tends to rise but the albumin globulin ratio does not vary greatly and the body fluids show no gross disturbance of electrolyte concentrations These relatively normal findings probably indicate the far more localized involvement of connective tissue (through which as quoted above all extracellular processes must be mediated) than in generalized lupus Diagnostic difficulties in the alimentary tract arise from this localization John stone (1952) referred to the possible occurrence of scleroderma like lesions in the pharynx and oesophagus in dermatomyositis and Talbott and Ferrandis (1956) stated that the two conditions may be indistinguishable though changes in dermatomyositis are considerably less frequent Diagnosis rests on the histological findings in biopsy of altered skin and muscle repeated if necessary several times

**Treatment**

At present the use of ACTH or adrenal steroids is the method of first choice No specific measures to deal with disorders of the alimentary tract have been recommended but precautions against oesophageal spill over and search for developing neoplasm are advisable With steroid therapy dietetic measures against peptic ulceration alkali medication and tests for occult blood in the stools may be wise

**Prognosis**

Talbott and Ferrandis (1956) stated that the disease is believed to be fatal in most instances O Leary and Waisman (1940) thought implication of the vital striated musculature (including the pharynx) to be an extremely serious com plication and it is likely that when gastro intestinal lesions are present the outlook is very bad However before modern treatments were available Roxburgh (1944) considered there were milder cases in which the prognosis was favourable though skin changes and weakness from loss of muscle tissue were permanent In such cases the alimentary tract may be involved more frequently than is realized Although the fulminating form of the disease brings death rapidly the average expectation of life is approximately 3 years and considerably longer survival has been observed In these cases pharyngeal and oesophageal lesions may lead to aspiration pneumonia and terminal infection and search for such sequelae may enable precautionary measures to be taken

The presence of a malignant tumour does not appear to affect the ultimate prognosis (Talbott and Ferrandis 1956) Although amelioration of the symptoms and signs of dermatomyositis may follow treatment by removal irradiation or chemotherapy of the growth the improvement does not seem to be either constant or permanent

## SCLERODERMIA (SYSTEMIC SCLEROSIS)

Klingman (1930) stated that scleroderma as an entity was scoffed at by most authorities and there was at that time a necessity for Parkes Weber s differentiation between sclerodermia or systemic sclerosis (Goetz 1945) now regarded as a

collagen disease and the symptomatic sclerodermas in which sclerotic skin-changes follow a variety of *conditions circulatory endocrine or traumatic Connective* tissue may respond locally and so to speak symptomatically to various and often local stimuli by changes which macroscopically and even microscopically resemble the more generalized lesions of the essential and systemic disease sclerodermia It has been necessary to separate these lesions due to oedema erythema induratum dysthyroidal states panniculitis fat sclerosis and pruriginous dermatoses from the two main varieties of sclerodermia the circumscribed guttate or morphoeic and the generalized There is also doubt about the unity of the generalized form itself One of its sub varieties begins insidiously and attacks first the upper part of the body spreading until in months or years the greater part of the body surface is involved the skin bound down and the joints and muscles so fixed as to interfere with eating swallowing respiration and movements of viscera The other variety begins like Raynaud s disease affecting several fingers or a hand or both hands After months or years the skin of the distal phalanges becomes sclerotic the fingers shrunken and the joints fixed (Roxburgh 1944) Radiological examination shows absorption or occasionally sclerosis of the phalanges and subcutaneous calcinosis

This latter variety of generalized sclerodermia has been distinguished from the former on grounds of sex onset distribution prognosis and visceral lesions (Truelove and Whyte 1951) The visceral lesions in this variety or actually different disease involve especially the digestive tract though they are widespread and to the condition the terms systemic scleroderma or progressive systemic sclerosis have accordingly been applied instead of sclerodactyly or acrosclerosis as formerly

**Clinical manifestations**

It is common for Raynaud s phenomenon to have been present for many years before the patient becomes aware of any disturbance of the alimentary tract and indeed functional and organic abnormalities of the tract itself particularly of the oesophagus are quite often present without the patient s knowledge In other cases consciousness of delay at the cardia retrosternal pain vomiting and severe loss of weight may be the presenting symptoms These may arise rapidly and almost complete inability to swallow develops in weeks or months In a case of Professor Grey Turner s with only 6 months history of Raynaud s phenomenon operation was necessary to relieve dysphagia If delay is suspected auscultation over the epigastrium following a drink of water in the prone position may demonstrate it considerable prolongation of the usual 10 seconds wait being necessary before the characteristic sounds are heard Oesophagoscopy is usually difficult but if performed shows leukoplakia patchy oesophagitis and frequent stricture Gastroscopy has been reported to show pearl white smooth glistening mucosa surrounding the cardia apparently similar in appearance to the oesophageal leukoplakia (Palmer 1949)

Symptoms of intestinal involvement constipation more often than diarrhoea frank steatorrhoea distension and rarely obstruction may develop Sigmoidoscopy shows a peculiar pale dry grey rather rigid wall of the rectum and lower sigmoid colon regarded as a characteristic appearance in the disease (Cullinan 1953) Rectal ulceration has also been reported

**Radiological appearances**

The appearances in this condition as they affect the pharynx and oesophagus have been described by Johnstone (1952) In his account he included a case which had been diagnosed as dermatomyositis in which there was defective swallowing mechanism apparently normal oesophageal peristalsis and hiatal hernia with oesophagitis and Talbott and Ferrandis (1956) made a similar report The liability of dermatomyositis to involve the pharyngeal and palatal muscles has been commented on above and it is of interest that the report by Ehrmann (1903) which is usually stated to be the first on the subject of scleroderma with oesophageal involvement might be interpreted as dermatomyositis and that on endoscopy a tumour was suspected a possibility which adds further interest

Since Johnstone s observation that careful examination of the pharynx and upper oesophagus was desirable in scleroderma confirmation has been provided (Ardran et al 1953) By ciné radiograph studies 7 patients with acrosclerosis were compared in upright and supine positions with patients showing non scleroder matous Raynaud s phenomenon with other patients having slight scleroderma and with 1 patient having a long history of stomatitis pharyngitis and oesophagitis leading to fibrotic strictures dilated satisfactorily at the time of examination In these control patients no disorder of the tongue pharynx or oesophagus was detected but in those with acrosclerosis the recognized difficulty in taking masti cating and swallowing food was well demonstrated It appeared to be due largely to limitation of the normal movements of elevation of the tongue and excessive backward projection of its dorsal surface Marked elevation of the soft palate contributed to the disability The force of gravity was needed to spill the bolus into the mesopharynx and if this and elevation of the tongue did not suffice there was partial retention After passage through the hypopharynx the cricopharyngeal sphincter appeared to open normally but though pharyngeal muscular contractions were normal in 2 cases in others they were weak or absent

The larynx usually closed normally but in 2 cases barium entered the vestibule where it remained during three swallowing movements and in 1 patient was seen to enter the trachea

The mode of passage through the oesophagus was the same in 4 patients who showed abnormal swallowing In all these the primary propulsive wave disappeared just above the level of the sternal notch There was no delay at the cardia in the erect position except in 1 patient When these 4 patients were examined in the horizontal position however the time for transit of barium from the oesophagus to the stomach was much prolonged and amounted in 2 cases to half an hour Ardran et al (1953) emphasized the significance of defective pharyngeal clearance when oesophageal retention is present since it will be likely to lead to the spill over into the trachea later demonstrated by Kemp Harper (1953)

*Oesophageal function*

Disorder of oesophageal function in scleroderma has been investigated by Dorn horst et al (1954) by simultaneous radiography and intra oesophageal pressure measure ments Pressure readings confirmed the ciné radiographic findings of Ardran et al (1953) that propulsive waves failed to continue normally into the lower half of the oesophagus The upper half contracted with normal vigour though usually more briefly and often with spontaneous iteration but the contraction either failed entirely

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to propagate or became very feeble and inco ordinate It is pointed out that this disorder occurred in patients with sclerodactyly who were free from dysphagia and that the association may easily be overlooked particularly if the radiological examination is conducted in the standing position and a barium cream of average consistency is used Lower oesophageal weakness was demonstrated radiographically if a thin barium emulsion (specific gravity 1 2) was swallowed in the supine slightly head down position when the bolus was carried to about the position of the tracheal bifurcation At this point progress ceased and though a further mouthful might push the barium on a little it would enter the stomach only when the patient stood

Recent radiological examination of the intestine has shown far more frequent involvement of the colon than of the small intestine (Kemp Harper 1953) In the colon changes are easier to demonstrate and asymmetry with haustration on one side and a wide mouthed diverticulum on the other may be striking In a minority of cases the small intestine showed delay in motility and occasional out pouchings

**Pathology**

Laboratory examinations rarely contribute to the diagnosis of the primary disease few of the characteristics of other collagen diseases being present Occasional changes in the serum protein concentrations have been reported but must be uncommon There may be a flat glucose tolerance curve if intestinal activity is impaired

Various histological changes in the alimentary tract have been described Dorn horst et al (1954) found simple atrophy of the main oesophageal musculature with minimal fibrotic replacement and cases observed personally show similar appearances However other observers report localized muscular hypertrophy with swelling degeneration and fibrous replacement of the circular and longitudinal fibres (Goetz 1945) coagulative necrosis loss of striation and granular cytoplasm of the muscula ture of the tongue pharynx oesophagus and intestinal wall with no proliferation of collagenous tissue between the muscle bundles (East and Oram 1947) or atrophy of the true muscularis which was surrounded by extremely dense collagenous tissue (Abrams et al 1954 Goetz 1945) It is clear there is no constant histological pattern in the oesophageal wall The oesophageal epithelium may show thickening if leukoplakia has been present or thinning interruption and round celled infiltration if ulceration or oesophagitis have been present Histological findings are more consistent in the bowel perhaps because complicating peptic lesions are absent Loss of muscle thicken ing and cellular infiltration of the submucosa and in general hypertrophy of the connective tissue are present (Kemp Harper 1953) Muscular atrophy involves both longitudinal and circular coats (Abrams et al 1954 Goetz 1945) and accounts for the paper thin translucent appearance of the bowel wall which may perforate if necrosis and ulceration of the mucosa is present Local pouchings and narrowing of the oeso phagus and bowel have been attributed to lesions of the mesenteric plexus but these are not constant though the disease may occasionally damage them in its progress

**Diagnosis**

Sclerodermia with visceral involvement otherwise known as acrosclerosis sclerodactyly or progressive systemic sclerosis can indeed when fully developed be recognized more readily on clinical examination than any other collagen disease (Talbott and Ferrandis 1956) The gastro intestinal disturbances of function and anatomy which it produces are also often characteristic and constant and their association with Raynaud s phenomenon or in later stages with cutaneous atrophy of the hands and face leaves little doubt about the diagnosis Radiological examination of the hands and the oesophagus is usually suffic ent in cases which are at all advanced

At the same time the lesions demonstrated in the oesophagus by radiography can certainly be matched in patients with sliding hiatal hernias and oesophagitis It is difficult not to feel that the primary manifestation of the disease in the oeso phagus is in the early stages at any rate—and like the associated Raynaud s phenomenon—a disturbance of function The observations of Ardran and his colleagues and Dornhorst and his colleagues indicate this and it may be that impaired contractile power in the muscles of the oesophageal wall and of the upper and lower pinch-cocks of the oesophagus causes a failure to maintain sufficient intra luminal pressure to resist reflux of gastric contents When this occurs there may be a sudden exacerbation of symptoms so that rapid development of oesophageal obstruction may suggest neoplasm Alternatively slow development of non specific oesophagitis ulceration and hiatal hernia gives the various appear ances found in that syndrome

### Treatment

Although there is evidence that cortisone or corticotrophin therapy may relieve the symptoms of sclerodermia it appears that cases likely to respond are those in which vasomotor disturbances are absent (Zion et al 1955) Since visceral lesions are more frequent when vasomotor disturbances are present no benefit would be expected and experience in several cases treated personally is in agreement The element of oesophagitis present in some cases probably makes steroid therapy hazardous In one such case administration of cortisone was followed by a very severe oesophagitis necessitating gastrostomy

Localized scleroderma has been relieved occasionally by the use of cinchoninic acid derivatives (Rennie et al 1951) Personal trial in 6 cases showing oesophageal lesions gave no evidence of improvement

Beneficial treatment of the oesophageal lesions seems best directed to the usual management of oesophagitis with an adequate supply of calorie protein and vitamin requirements Obstruction can be safely dealt with surgically in suitable cases dilatation or operation having been justified in 4 cases seen personally Sympathectomy has been of no benefit (Cullinan 1953)

When the bowel is involved treatment has to be empirical and medical directed as far as possible to any anaemia or steatorrhoea or vitamin deficiency that presents The lesion is diffuse and surgery is not indicated

## THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura is rare though it will probably be in creasingly recognized The basic lesion is at present thought to be an accumulation of hyaline material beneath the endothelium of arterioles and capillaries which protruding into the lumen of the vessel becomes covered by platelets Diagnosis is made by finding the lesion in aspirated bone marrow specimens or in skin and muscle material

Fever and indefinite symptoms of malaise joint pains nausea and vomiting are followed by purpura anaemia and jaundice The anaemia is haemolytic in type Hepatomegaly and splenomegaly are present in 50 per cent of the cases and central spinal or peripheral neurological symptoms are frequent

Haematemesis and melaena do not appear to occur independently of generalized purpura though present in about 20 per cent of published cases Changes in serum protein levels may affect liver function tests and serum bilirubin levels are raised but no primarily gastro enterological conditions seem to have entered the differential diagnosis Mesenteric thrombosis has occurred in the course of the disease but operative measures are regarded as hazardous because of purpura

## HENOCH S PURPURA

In Henoch s purpura there is a generalized disturbance of the small blood vessels which may show fibrinoid change endothelial swelling or perivascular inflammatory exudate

The condition manifests itself by abdominal pain purpura and an erythematous exanthem with which may be associated urticaria joint pains or evidence of *nephritis Its most striking symptom is the abdominal pain due to oedema and* often haemorrhage involving the wall of the bowel and producing colic vomiting and blood in the stools The cause is unknown but hypersensitivity to bacterial infection has been suggested or allergy to items of food Very rarely evidence supporting the latter is obtained

In general no aetiology can be fully proved When the skin lesions do not appear until after the abdominal symptoms diagnosis may be impossible though inquiry should be made for a previous history of the various elements in the syndrome Many laparotomies have been performed and the condition found is usually the above mentioned oedema and haemorrhage into the wall of the gut Whitmore and Peterson (1946) pointed out that haemorrhage into the mucosal layer would obliterate the mucosal folds and in severe cases cause separation of patches of mucosa and ulceration They reported a case in which examination by barium meal demonstrated irregularities in calibre and outline of the small bowel with loss of mucosal pattern

A number of similar reports has been published In general there is hypomotility rather than the hypermotility of enteritis Gastric emptying tends to be delayed Abnormal appearances may begin in the duodenum which shows spasm dilatation or irregularity and the mucosal pattern particularly in its terminal region and throughout the small intestine tends to be lost The loops of small bowel show abnormal segmentation and marginal definition is obscured with occasional suggestions of ulceration or early diverticulum formation These appearances have in several cases preceded the appearance of the skin rash and have disappeared in from 4 to 12 weeks

Unlike the commonly associated nephritis joint swellings and intestinal bleeding seldom recur in the natural course of the disease It is not considered that corticotrophin and cortisone are of any value (Philpott and Briggs 1953)

## RHEUMATOID ARTHRITIS

Rheumatoid arthritis is classified among the collagen diseases because of its tendency to show from time to time the vascular lesions lymphadenopathy raised *gamma* globulin nodules fibrinoid necrosis serositis and arthritis which are present with occasional exceptions but much greater severity in the full blown members of this group

When it appears in its common and pure form gastro intestinal complications or manifestations are very rare indeed However it has complex relations with generalized lupus erythematosus and polyarteritis nodosa in which gastro intestinal lesions have already been described The condition may develop as a complication of ulcerative colitis or be associated with Sjogren s syndrome in which lesions of the alimentary tract are undoubtedly present and which have been previously considered It is probably the commonest cause of amyloid disease in which the liver is very often affected Thus in various indirect ways rheumatoid arthritis has its gastro-enterological influences

Some 20 years ago the problem was looked at the other way round entirely and a very important causal factor of the disease was considered to be some general abnormality of the gastro intestinal tract Extensive series of post mortem examinations make no mention of significant gastro intestinal lesions in the uncomplicated disease though Cruickshank (1954) found 2 cases in which vessels closely associated with the oesophagus were considered to show the changes of rheumatoid arthritis

However when polyarteritis nodosa complicates rheumatoid arthritis ulceration of the stomach and bowel is frequent and vascular lesions practically invariable Fatal haematemesis and melaena have also been reported in rheumatoid arthritis complicated by amyloid disease and terminated by uraemia

The incidence of amyloid disea e in an unselected series of hospital patients with rheumatoid arthritis is about 4 per cent (Fearnley and Lackner 1955) and the liver has been involved in all cases where autopsy or biopsy has been possible It is of no clinical importance except diagnostically and all liver function tests are normal

It may perhaps be added that a survey by the National Institutes of Health in the United States of America revealed that in a series of arthritic patients receiving cortisone over a period of years the incidence of ulcer approximated 35 per cent and that tests for occult blood are routine in many rheumatic clinics It is perhaps surprising that an alternative treatment giving aspirin orally in high dosage aiming at 1 grain per pound of body weight per day has not in some years of personal experience been associated with haematemesis There has seemed no doubt however that a third therapeutic agent phenylbutazone has been responsible for several haematemeses and perforations of peptic ulcers and occasionally jaundice with liver function tests indicating biliary tract obstruction The iatrogenic complications of rheumatoid arthritis may be appreciably gastro-enterological

## ACUTE RHEUMATISM

To complete the list of commonly included diseases it has been found that perivascular granulomas are present in the intestinal submucosa and connective tissue of the muscle coat in rheumatic fever (Svartz 1956) Digestive disturbances are however notoriously insignificant and rare Henoch s purpura may be associated but as in rheumatoid arthritis gastro intestinal symptoms are likely to be iatrogenic

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# CHAPTER 5

# CANCER OF THE ALIMENTARY TRACT

## I Aetiology of Cancer of the Stomach

RICHARD DOLL

## INTRODUCTION

LITTLE is known about the direct cause of cancer of the stomach but a great deal has been learned about the predisposing causes which form the background to its development For the purpose of discussion these causes may be classed under three headings (1) constitution (2) local gastric factors and (3) external environment The classification is however arbitrary and some factors might be classed under two headings while others in one group may be dependent for their effect on the presence of further factors classed in another group

## CONSTITUTION

**Heredity**

That heredity may play a part in determining the susceptibility to gastric cancer has long been suspected Accounts have been published of families in which a remarkably high proportion of the members suffered from the disease (including the family of Napoleon Bonaparte) these have been reviewed by Maimon and Zinninger (1953) The evidence has recently been strengthened by comparison of the incidence of the disease in the families of gastric cancer patients with that in the families of other patients or in the whole population of a region or country By such methods Videbaek and Mosbech (1954) in Denmark and Macklin (1955) in the United States of America estimated that the disease was some 3–4 times commoner in the affected families Other workers in the United States of America (Hagy 1954 Woolf 1955 1956) have however estimated that the familial incidence is only about twice normal and in view of the methods used this latter estimate would seem likely to be the more accurate

*Familial environment*

Some of the familial excess is probably due to a common familial environment but in view of the known association between gastric cancer and the possession of a specific blood group substance some is undoubtedly genetic in origin Whether these two factors together with perhaps an hereditary tendency to achlorhydria are sufficient to account for the apparent variation in susceptibility is not clear it may well be that other and important genetic factors are still to be discovered

*Racial factors*

The existence of major racial differences in susceptibility has not been proved The most striking apparently racial difference to have been recorded is that between the Indonesian and Chinese residents in Java This was brought to light when Snijders and Straub (1923) reported that gastric cancer formed only 1

per cent of all cancer seen among the Javanese while it accounted for 19 per cent of cancer among the Chinese A similar difference was subsequently reported by Kouwenaar (1951 1955) in Sumatra The conditions of life to which the two races were exposed were largely similar but it is not impossible that some environmental factors (for example in the diet or the methods of cooking) may have been responsible for the findings

Little difference in incidence has been recorded between the white and the Negro races when the two races are exposed to similar environments It has certainly been much less than the difference between sections of the same race when these are living under different conditions

**ABO blood group**

The surprising association between gastric cancer and the possession of the A blood group substance was first discovered by Aird et al (1953) since then it has been confirmed by several other groups of investigators in Great Britain Denmark Switzerland and the United States of America The results obtained in some 6 000 cases and 100 000 controls are summarized in Table I On average the incidence among persons with group A substance relative to that among persons of group O is 1 19 to 1 It is striking that the relative incidence found between persons of groups A and O in Basle and Copenhagen is similar to that found in Great Britain although the normal distribution of blood groups in Switzerland and Denmark is appreciably different from that in Great Britain

In Glasgow Sydney and Vienna no appreciable difference has been found between the incidence in groups O and A but when all the series are considered together it can be shown that the variation from place to place is not significant so that there is as yet no reason to believe that the effect of the factor varies in different parts of the world

According to two of the latest reports the significance of the blood group may vary with the site of origin of the cancers within the stomach (Jennings et al 1956 Billington 1956) Both these reports agree that the greatest excess of patients in group A occurred when the site of origin of the cancer was in the antrum (or pre pyloric region) they differ however in that for other gastric cancers Billington found an excess of patients of group O while Jennings and his colleagues found the distribution of groups to be essentially normal Both series are small and the results need confirmation they may however be of considerable importance since they imply that the blood group substance could be a major factor in the aetiology of one particular type of the disease According to Billington s data pre pyloric cancer could be 3 times as common among persons of group A as among those of group O

The mechanism by which one blood group can confer an increased susceptibility to gastric cancer (or another an increased resistance) is unknown If as appears likely the same relative incidence between the groups is found in many countries it will be difficult to believe that there is not a special strain within the population which carries both a high susceptibility to gastric cancer and a high incidence of A substance It could be that the genes which control the development of the blood group substances also participate in the development of the normal physiological reactions of the gut A simpler explanation however is derived from the fact that group substances of the ABO and Lewis systems usually appear in the

gastro intestinal secretions and probably constitute the principal source of soluble gastro intestinal mucus persons of group O usually secrete one substance (H) while persons of groups A B and AB usually secrete their specific group substances in addition Chemically the substances are muco polysaccharides and although they resemble one another closely their molecular sizes and the proportions and

TABLE I

RELATIVE INCIDENCE OF CARCINOMA OF THE STOMACH IN PERSONS WITH BLOOD GROUP A COMPARED WITH PERSONS WITH BLOOD GROUP O COLLECTED SERIES

| *Centre* | *Carcinoma* | | *Controls* | | *Relative incidence* | | *Authors* |
|---|---|---|---|---|---|---|---|
| | O | A | O | A | A | O | |
| Birmingham | 37 | 57 | 458 | 442 | 1 6 | 1 | |
| Leeds | 97 | 104 | 11 359 | 9 805 | 1 31 | 1 | |
| Liverpool | 85 | 97 | 462 | 402 | 1 31 | 1 | Aird et al (1953) |
| Manchester | 343 | 349 | 4 532 | 3 775 | 1 22 | 1 | Aird et al (1954) |
| Newcastle | 44 | 44 | 6 598 | 5 261 | 1 25 | 1 | |
| London | 578 | 617 | 4 578 | 4 219 | 1 16 | 1 | |
| London | 32 | 55 | 1 070 | 1 073 | 1 8 | 1 | Walther et al (1956) |
| Glasgow | 159 | 104 | 3 853 | 2 485 | 1 01 | 1 | Wallace (1954) |
| Sydney | 116 | 97 | 14 672 | 11 514 | 1 07 | 1 | Billington (1956) |
| Basle | 255 | 374 | 1 882 | 2 036 | 1 36 | 1 | Hollander (1953) |
| Copenhagen | 141 | 212 | 5 804 | 6 299 | 1 39 | 1 | Køster et al (1955) |
| Iowa | 383 | 416 | 2 892 | 2 675 | 1 2 | 1 | Buckwalter et al (1956) |
| Vienna | 415 | 505 | 3 631 | 4 422 | 1 0 | 1 | Speiser (1956) |
| Total all areas | 2 680 | 3 031 | 61 791 | 54 308 | 1 19 | 1 † | |

Aft r R berts J A F (1957) mod fi d by the dd t f f esh d t

† Obt ed f m th we ght d ge f th d d l se by th m h d mm ded by W lf (1955 )

configurations of their chemical components are distinct and it is conceivable that they react differently in the presence of certain external carcinogens Not all persons who possess a given group substance possess the ability to secrete it and it may be that a stronger association will be observed between the susceptibility to gastric cancer and the muco polysaccharides in the secretions than has already been observed with the group substances in the blood There is as yet no direct evidence on this point but Clarke et al (1956) have shown that this is true of another gastro intestinal condition—that is duodenal ulcer

**Sex factors**

In all countries and at all periods for which data are available the mortality and it seems certain the incidence of gastric cancer has been less in women than in men but the difference has not been great Recent mortality figures for 14 national and racial groups are shown in Table II in all these instances the range of female mortality varies only between 43 and 66 per cent of the male mortality It may be that this difference is due to a constitutional difference in susceptibility of the two sexes but from our knowledge of other types of non endocrine cancers it is also possible that it is the result of consistent differences in dietetic or other personal habits It might for example be due in part to simple quantitative differences in

TABLE II

MORTALITY FROM CANCER OF THE STOMACH IN DIFFERENT COUNTRIES

| *Country* | *Period* | *Equivalent average death rate per 100 000 persons (aged 35–74 years)* * | | *Female rate (per cent) as per cent of male* |
|---|---|---|---|---|
| | | *Men* | *Women* | |
| Japan | 1951 | 220 | 112 | 51 |
| Finland | 1951–3 | 216 | 122 | 56 |
| Iceland | 1940–9 | 209 | 130 | 62 |
| Norway | 1952 | 131 | 66 | 50 |
| Netherlands | 1950–2 | 116 | 70 | 60 |
| Denmark | 1951–2 | 96 | 56 | 58 |
| France | 1952 | 94 | 51 | 54 |
| England and Wales | 1951 | 91 | 48 | 53 |
| Sweden | 1952 | 90 | 60 | 66 |
| Israel | 1951 | 86 | 57 | 66 |
| United States of America | | | | |
| (non whites) | 1952 | 76 | 33 | 43 |
| (whites) | 1952 | 48 | 24 | 50 |
| Canada | 1950 | 75 | 39 | 52 |
| Venezuela | 1950 | 65 | 43 | 66 |

Cal l ted from dat ollect d by N de b g (1955) o p bl h d n the n t al t l t t t cs The meth d of c lcul t on of the eq i al t erag death t n th foot ot to p g 59

the amount of food eaten and hence in the degree of exposure to any carcinogenic factors ingested at the same time

## LOCAL GASTRIC FACTORS

**Gastritis, pernicious anaemia and achlorhydria**

The view that gastritis is a precursor of gastric cancer has been accepted by in dividual pathologists for many years (Konjetzny 1913 Orator 1925) while Hurst (1929) believed that the presence of chronic gastritis was the most common condi tion predisposing to the disease and also accounted for the common association of the disease with achlorhydria The concept of chronic gastritis is not an easy one to define but it is clear from all reports that atrophy is the primary feature of the type of gastritis which is often associated with cancer in the presence of atrophy the test meal usually but not invariably shows achlorhydria and it has recently been shown that glandular mucoprotein is also absent from the secretions (Wolf et al 1953) It seems probable that metaplasia of the surface epithelium and gastric glands to an intestinal type of epithelium (with goblet and Paneth cells) is an important histological characteristic of this type of gastritis (Morson 1955a and b) Metaplasia is however not confined to patients with carcinoma of the stomach but is found in an extreme form with pernicious anaemia to a lesser degree in stomachs resected from patients with gastric ulcer and on occasions in patients without any gross gastric lesion It is notable that a high incidence of intestinal metaplasia was observed in the stomach of the Chinese in Java whereas the condition was rare among the Indonesians among whom gastric cancer was also rare (Bonne et al 1938)

Hurst s view that achlorhydria is a precursor rather than an accompaniment of cancer has largely been developed by workers at the Mayo Clinic Comfort (1951) after reviewing the evidence concluded that it tends to support the hypothesis that atrophy of the gastric mucous membrane plays an important role in the de pression of mean gastric secretory activity before the development of cancer and the atrophic gastric mucosa is a soil in which cancer frequently develops Berkson et al (1956) have now demonstrated the clinical significance of these conclusions by following up—15 or more years after hospital investigation—a group of over 800 patients who had had achlorhydria without having had either pernicious anaemia or gastric cancer at the time of the first examination They have also similarly followed a group of over 200 patients in whom achlorhydria was associ ated with pernicious anaemia Their results show that whereas the total number of deaths in each group was close to the number expected from the mortality recorded in the whole country the number of gastric-cancer deaths was about six times the number expected To some extent the excess deaths from gastric cancer may have been due to a greater readiness to diagnose the disease in patients already known to have achlorhydria but this is unlikely to account for them all Several other workers have recorded an incidence of gastric cancer in patients with pernicious anaemia of about three times normal (Kaplan and Rigler 1945 Mosbech and Videbaek 1950 Jorgensen 1951) and clinical data suggest that a similar excess of gastric-cancer deaths may be expected in simple achlorhydria *

If these latter figures are accepted it follows that the incidence of gastric cancer must be approximately eight times higher in persons with clinical achlorhydria than in persons in whom gastric secretion is less severely depressed Whether the patient also suffers from pernicious anaemia appears to be unimportant and in the present state of knowledge it seems reasonable to attribute the high incidence in both groups to an underlying chronic atrophic gastritis

## Gastric polyps

Polyps are uncommon in the stomach Schindler (1950) reported an incidence of 2 per cent in all persons coming to gastroscopy and their incidence in normal persons must be very much lower They are however found more frequently in persons operated on for cancer of the stomach in patients with pernicious anaemia and in the presence of achlorhydria Carcinomatous zones have frequently been observed in individual polyps and it must be concluded that an adenomatous polyp in the stomach is potentially a pre malignant condition (Edwards and Brown 1950 Morson 1955c) The frequency with which malignancy occurs may not be great and Cary and Hay (1950) have been able to follow 30 patients with gastric polyps for up to 9 years without seeing one develop into a cancer

## Gastric ulcer

That cancer of the stomach may on occasions arise in the edge of a chronic gastric ulcer cannot be denied such a development must even be anticipated in view of the natural history of chronic ulceration elsewhere in the body Clearly however malignant degeneration must be uncommon or the possibility of its

* A ces f h d w ld o f two-th d f he ses f g ce d l ped in patien w th hl hyd ia d ne-fif h f ll perso f h orrespo d g ges h d hl hydn f h se h nc dence mo g achlorh d ic t t h t h h t pop l w ld be ⅓ – ½ l h i 3 3 t l

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| Israel | 1951 | 86 | 57 | 66 |
| United States of America | | | | |
| (non whites) | 1952 | 76 | 33 | 43 |
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| Canada | 1950 | 75 | 39 | 52 |
| Venezuela | 1950 | 65 | 43 | 66 |

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peptic ulceration in a stomach wall weakened by the presence of a cancer and that the cancer is sufficiently slow growing to enable the signs of chronicity to develop in the ulcer

Whether such appearances of chronicity could be produced in one or two years is not clear but patients with benign ulcers which are pathologically very chronic certainly give a history of a year or less on occasions

It is impossible to decide how important the contribution of benign ulcers may be to the pathogenesis of gastric cancer It is not large but if it accounted for only 5 per cent of all the cancers it might still be an important cause of that proportion of cancers found against a background of an actively secreting mucosa

## EXTERNAL ENVIRONMENT

### Decrease in mortality

One reason for believing that environmental factors are of importance in the production of gastric cancer is that in several countries a substantial reduction has been recorded in the mortality attributed to the disease For example in the United States of America the equivalent average death rate from gastric cancer for men aged 35–74 years was in 1952 45 per cent less than it had been in 1930 * Similarly in Norway the rate had been reduced by 30 per cent and in the Netherlands between 1939 and 1951 it had been reduced by 31 per cent In England and Wales on the other hand the change in mortality has been comparatively slight Between 1913 and 1933 the death rate increased by 13 per cent but during the next 20 years it fell steadily and in 1954 it was 3 per cent less than it had been 40 years before In recent years there has not been an appreciable increase in mortality in any country

When different age groups are considered separately it is found that the extent of the decline has been greatest in the younger age groups while it has as yet hardly or not at all affected the older age groups In view of the long induction period for most types of cancer it must be expected that reduction in the prevalence of any external agents capable of producing cancer would first show itself by a reduction in the mortality of the younger ages and the observed changes in mortality are therefore consistent with the idea that the reduction is in part due to a decreased exposure to such agents

It is true that a greater proportion of cases may now be regarded as operable but the prognosis in the average case is so bad that it cannot be claimed that any major proportion of the reduction in mortality is due to a reduction in fatality

### Geographical variation

Major differences are recorded in the mortality from gastric cancer in different countries A selection from the available data is shown in Table II

The maximum rates are seen to occur in Japan Finland and Iceland in these [illegible]

occurrence would not still be disputed by physicians who have had the clinical care of hundreds of gastric ulcer patients In fact very few authenticated cases have been recorded and the hypothesis that malignant degeneration in a chronic ulcer is a relatively important cause of gastric cancer is derived entirely from *pathological considerations*

Much time has been given to studying the histological appearances of ulcer cancers and strict criteria have been evolved for their diagnosis (Newcomb 1930 Stewart 1955) The great difficulty lies in distinguishing between a chronic *ulcer in the edge of which a cancer has developed and the occurrence of an ulcer in* tissue devitalized by the presence of a spreading cancer In Stewart s view the presence of a *chronic* gastric ulcer effectively rules out the second possibility and so long as the cancer is sufficiently closely related to the ulcer he believes that the positive diagnosis of a chronic ulcer is sufficient to justify the diagnosis of an ulcer cancer On this basis Stewart found that ulcer cancer was present in 103 out of 1 503 gastrectomy specimens personally examined at Leeds during the years 1921 to 1949 of the other specimens 922 showed a simple chronic ulcer 465 showed a primary gastric carcinoma and 13 showed the presence of both lesions unrelated to one another That is to say 10 per cent of the chronic gastric ulcers examined showed related cancer and 18 per cent of the cancers had arisen in a chronic ulcer To check his conclusions Stewart compared the clinical and surgical findings in the three groups of cases classified on histological grounds and found that the duration of symptoms the acidity of the gastric contents and the tendency for the lesion to tear on surgical removal were similar in patients with ulcer cancer and in patients with chronic gastric ulcers Both groups of patients were in these respects sharply distinguished from the patients with primary gastric cancer On the other hand the site of the lesion in ulcer cancer was intermediate between the other two groups

The difficulty in accepting such results at their face value lies solely in the rarity with which the transformation is observed during the follow up of gastric ulcer patients treated medically It must be realized however that even though gastric cancer is responsible for almost 3 per cent of all male deaths it has a high fatality rate and its annual incidence in a given population is low In England and Wales only about 1 man in every 1 000 aged 45 years and over can be expected to develop the disease during the course of a year so that even if one sixth of all gastric cancers arose in chronic ulcers only about 3 out of 1 000 ulcers would be expected to become malignant annually and this proportion would not be easy to detect Swynnerton and Tanner (1953) in their follow up study of gastric ulcer patients treated medically found that 3 out of 262 had died of cancer of the stomach and 3 others had developed it in some 2 000–3 000 years of observation These figures are compatible with either the hypothesis that *no* ulcer degenerates or that an appreciable proportion (say 10 per cent) of cancers arise from ulcers Swynnerton and Tanner thought that the original diagnosis of a benign ulcer was erroneous in 2 of their cases and they preferred to ascribe the association between ulcer and cancer (if one exists) to a preference of both for the same soil That there may be a similarity of soil is perhaps suggested by the finding of a high prevalence of intestinal metaplasia in the stomachs of patients with chronic gastric ulcers (Morson 1955a) If this is so it must be presumed that the observations of Stewart and of many other experienced pathologists result from the occurrence of secondary

45 per cent and 56 per cent—of the numbers expected from the data for the white population That is the mortality among the Bantus was about 50 per cent of that recorded for the population with the lowest mortality in Table II

Even within the boundaries of a single country substantial differences have been recorded Thirty years ago the mortality from gastric cancer in North Wales was more than double that in the south east of England and a similar difference stil exists Stocks (1954) found that the proportion of cases confirmed by operation or radiography in North Wales was much the same as in the neighbouring region with a lower mortality and it is probable that the difference is a real one Regional differences have also been recorded in other countries in the United States of America for example the cancer survey of 1947 confirmed that gastric cancer was 50 per cent commoner in the north than in the south (Dorn and Cutler 1955)

**Urban rural differences**

Differences in incidence between town and country are in general not marked Early in the century it was the rule for higher rates to be reported from rural areas but this excess has now generally disappeared It still persists in Denmark (Clem mesen and Nielsen 1952) but in Finland there is practically no difference (Saxén 1955) and in Norway and in England and Wales the rate has become slightly higher in the towns (Pedersen 1957 Stocks 1947)

**Relationship to soil**

Several workers have sought to attribute regional differences to differences in the character of the soil Tromp and Diehl (1955) showed that the mortality from gastric cancer in the Netherlands was consistently higher in communities situated on peat soils than in those on sandy or on river-clay soils and they suggested that this might be due to a difference in the distribution of trace elements In this respect it may be recalled that Stocks (1924) found a positive correlation between alimentary cancer and goitre frequency in Switzerland and a similar correlation was subsequently noted in the United States of America (cited by Stocks 1947) Stocks is now carrying out a large scale investigation into the nature of the soil at the homes of persons dying of different types of cancer in North Wales and the surrounding counties and in a preliminary report (Stocks 1956) he has presented data to suggest that a certain high content of organic matter in the soil may be associated with the homes of patients with gastric cancer This observation is of particular interest since Davies and Wynne Griffiths (1954) independently found a similar characteristic to be associated with high gastric cancer incidence in Anglesey North Wales Presumably if a relationship with one or more specific types of soil is confirmed it must be interpreted as meaning that certain factors which are capable of inducing or preventing gastric cancer are transmitted from the soil to the local food or water supplies

**Socio-economic factors**

One of the most striking facts about the distribution of gastric cancer is its predilection for the poorer economic classes This is shown clearly by the reports of the Registrar General for England and Wales (1938 1954) When the male population is divided into 5 classes according to occupation and married women are classified according to the occupations of their husbands it is found that the

countries the death rate from gastric cancer is between 4 and 5 times as great as it is among the white population of the United States of America These differences cannot reasonably be attributed to differences in racial susceptibility The differences between the 4 Scandinavian countries and between the 3 English speaking countries weigh against such an explanation Nor does it seem that they can all be due to differences in standards of diagnosis or treatment Such an explanation might account for the position of some countries—in Venezuela for example the low rate is due to a disproportionately low rate in the older age groups and these are the groups which are most likely to be inadequately investigated—but it cannot surely account for the differences between Iceland Norway Sweden and the United States of America Evidence against such an explanation is moreover provided by the data collected in those countries which have established schemes of cancer registration A comparison between the incidence of gastric cancer recorded in such surveys in Denmark Finland and the United States of America and the mortality recorded from death certificates shows that the two sets of data agree closely irrespective of whether the recorded mortality is high or low (Doll 1956) It is therefore probable that the differences which have been shown reflect real differences and that they result from variations in the degree to which men and women in the different countries are exposed to environmental carcinogens

Even more marked differences would probably be recorded if detailed vital statistics were available for parts of Asia and Africa Clinical and autopsy series agree in showing that cancer of the stomach formed only a small proportion of all cancer in many of the countries with relatively undeveloped medical services but such data are very difficult to interpret Large differences may well be spurious and due to differences in the average age at death and the relative frequency of other diseases including other types of cancer

The available data were summarized and critically examined by Kouwenaar (1955) with the following conclusions

(1) The incidence of gastric cancer among Africans living under primitive African conditions was much lower than among Africans living in a highly civilized country

(2) The Malays of Indonesia and Malaya appeared to have a low incidence

(3) Among the Chinese on the other hand the incidence may have been much the same as among Europeans irrespective of whether the Chinese lived in Indo nesia Malaya or China

(4) In Vietnam the incidence was much lower in the south than in the north approximating in the south to that found among the Malays

Since Kouwenaar s report the first firm estimate of the incidence of cancer among a native African population has been made by Higginson and Oettle (1957) who studied the Bantu population of Johannesburg over the years 1953–1955 and were able to relate the cases discovered to the population at risk with some degree of confidence They showed that whereas the incidence of some types of cancer was the same as or appreciably higher than would have been expected from the mortality data available for the non white population of the United States of America the incidence of most types was appreciably lower For cancer of the stomach the numbers of cases found (41 in men and 19 in women) were respectively 31 per cent and 39 per cent of the numbers expected from the data for non whites in the United States of America and were about 50 per cent—that is

What factors do these diets share in common which are deficient from the diets in North America and from the diet eaten by the South African Bantu? Is it that North American diets contain some protective factor? If so it would be com prehensible that the incidence is generally low among the wealthier classes and that it has decreased recently in many parts of Europe

Whatever it may be it is difficult to see how the same factor could account for the difference between the Chinese and Malays in Indonesia According to Kou wenaar (1951) the principal foods of both are rice and fish but the Chinese some times eat pork and use fat freely while the Javanese sometimes eat beef and use vegetable oils

An observation that may have some bearing on the dietetic factors involved was made by Elkeles (1953) who reported that atherosclerosis as shown radio graphically by calcification of the abdominal aorta was appreciably less common in patients with gastric cancer than in other patients When allowance is made for differences in age distribution his figures indicate that calcification was present in 36 per cent of a group of patients without gastric pathology against 4 per cent among 70 gastric cancer patients A similar though less marked difference has been observed by Doll et al (1957) at the Central Middlesex Hospital London (unpublished data) In 161 cases of gastric cancer calcification was seen in 12 per cent while it was present in 29 per cent of a group of other patients of the same sex and age distribution examined for various non gastric conditions These findings recall the experience of Dungal (1953) that atherosclerosis is relatively uncommon in Iceland (despite the high fat diet) and that it is comparatively rare in Japan it is conceivable that dietetic factors antagonistic to one another are involved in the development of the two conditions

Methods of cooking may perhaps be of greater importance than the actual food employed The pyrolysis of organic matter by heat can produce many potent carcinogens (for example 3 4 benzpyrene) and such a reaction may be more likely to occur with one mode of cooking than with another Frying grilling and roasting cause different chemical reactions from boiling and stewing Moreover as Peacock (1956) pointed out the vessels used for cooking may also be significant Iron is a potent catalyst for heated fats and induces more vigorous reactions than for example aluminium or glass and Peacock found that cotton seed oil heated to 320 in the presence of iron was more carcinogenic for the fore stomachs of mice than the same oil heated in glass vessels without contact with iron Whether such an effect would also be reproduced in man is unknown but the results of his experiments suggest that even such a simple change in human habits as the in creasing use of non ferrous cooking vessels might exert an appreciable influence on the incidence of the disease

The temperature at which food is taken may also be relevant Direct evidence is inconclusive but the habitual drinking of over hot fluids may well contribute to the production of one of the conditions which predispose to the development of cancer—that is atrophic gastritis (Edwards and Edwards 1956)

**Alcohol and tobacco**

The abuse of alcohol is a factor which in view of its association with certain types of cancer of the pharynx and larynx might well be of aetiological importance In fact as has already been referred to men employed in the alcoholic trades show

mortality in the poorer groups is approximately three times as great as that in the wealthiest Similar results have been obtained at each of the three last censuses in 1921 1931 and 1951 the results are shown in Fig 13

A similar relationship with economic status has been observed in Norway (Rennaes and Ostberg 1955 and Torgersen and Petersen 1956) and to a somewhat



FIG 13 —Standardized mortality from cancer of the stomach in 5 socio economic classes

lesser extent in the United States of America (Cohart 1954) and Denmark (Clemmesen and Nielsen 1951) From a detailed study of gastric cancer in Connecticut Cohart (1954) concluded that it is impossible to attribute the differences in incidence to differences in either accuracy of diagnosis or completeness of reporting

**Occupation**

No occupation has been found to give rise to a special risk of the disease and no special risk results from employment in those trades which are associated with a high consumption of alcohol (Registrar General 1938)

**Diet**

It is natural to suppose that one of the principal environmental factors to affect the incidence of gastric cancer should be the nature of the food put into the stomach and that differences in dietetic habits can explain many of the differences in incidence which have been recorded In fact there is practically no evidence about the carcinogenetic effect of foods This is due partly to the fact that until the discovery that carcinoma of the stomach was a common cause of death in captivity of one species of rodent (Mastomys) no experimental animal was known to develop cancer of the glandular part of the stomach sufficiently often to be useful experimentally (Oettlé 1955) and partly because it is only recently that reliable epidemiological evidence has been obtained of the great differences in incidence which can occur among racially similar groups At a first examination it is extremely difficult to see what factors are shared in common by the diets eaten by people who suffer a high incidence and which are absent from the diets of those who have a low incidence According to Dungal (1955) food in Iceland is rich in animal protein and fat the staple foods are meat milk and fish—boiled or fried—with relatively great quantities of fat and fair amounts of bread and potatoes but with very little vegetables or fruit On the other hand the Japanese who suffer an even higher incidence of the disease eat diets which are extremely poor in fats and which consist essentially of boiled rice and vegetables with occasional fish—which is often eaten raw

What factors do these diets share in common which are deficient from the diets in North America and from the diet eaten by the South African Bantu? Is it that North American diets contain some protective factor? If so it would be comprehensible that the incidence is generally low among the wealthier classes and that it has decreased recently in many parts of Europe

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no greater mortality from gastric cancer than other employees and direct study of patients has confirmed that those with gastric cancer give histories of no greater alcohol consumption than those given by patients with other diseases (Stocks 1956)

Tobacco appears to be unrelated to cancer of the stomach irrespective of whether it is smoked in the form of cigarettes in a pipe or is chewed (Doll and Hill unpublished data)

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## II PRE MALIGNANT STATES OF THE COLON AND RECTUM

CUTHBERT E DUKES

THREE lesions of the colon and rectum are known to be followed frequently by cancer namely (1) benign epithelial tumours (2) familial colonic polyposis and (3) severe chronic ulcerative colitis *The evidence in support of this is briefly stated* and the initial phases of malignancy in each lesion illustrated because this is of the utmost importance in relation to surgical treatment It will help to avoid misunderstandings if certain terms in common use by pathologists when reporting on biopsies are first explained

### Definitions

*Irregular epithelial proliferation* —This may be reparative inflammatory or neoplastic in origin It is not necessarily a pre-cancerous lesion

*Carcinoma* in situ —This means that cells having all the typical morphological characteristics of carcinoma have been found in the sections but these malignant looking cells are still in their natural relationship with surrounding tissues and there is no evidence of either invasion or infiltration When the histological picture of carcinoma *in situ* is found it may be very difficult to decide whether this is actually the first stage of cancer or is only a transitory manifestation of local epithelial regeneration and repair In other words one cannot always say whether what appears to be carcinoma *in situ* will inevitably proceed to clinical cancer for this reason such cases should be either excluded from cancer statistics or if included placed in a special category *The view of the author is that they should be classed as doubtful lesions possibly of a* pre-cancerous character (Fig 14 (*a*) and (*b*))

*Focal carcinoma* — This term is used to describe a small focus of undoubted carcinoma but of microscopic dimensions and still limited to its site of origin and immediate surroundings (Fig 15) The difference between carcinoma *in situ* and focal carcinoma *should be clearly appreciated the former if left untreated may or may not proceed to* clinical cancer but the latter certainly will and should therefore be included in the statistics as cases of cancer and not as doubtful lesions Distinction should be made however between accidental findings and cases of known focal carcinoma deliberately treated by a local excision

*Invasive cancer* —A convenient term to describe a later stage in the development of a carcinoma invasive cancer implies that the malignant growth has proceeded beyond the focal stage and that there is now obvious infiltration and invasion of surrounding tissues (Fig 16) If invasive carcinoma is found unexpectedly in a supposed benign tumour removed by a local excision the question arises as to whether or not further surgical treatment is necessary immediately Much will then depend on the histology of the tumour and the evidence as to free margin In general it may be said that un differentiated or anaplastic tumours are not safely treated by local excision but well differentiated tumours which appear to be of a low grade of malignancy may often be successfully treated by a local operation only The progressive stages in the develop ment of carcinoma in a pre existing adenoma are represented diagrammatically in Fig 17

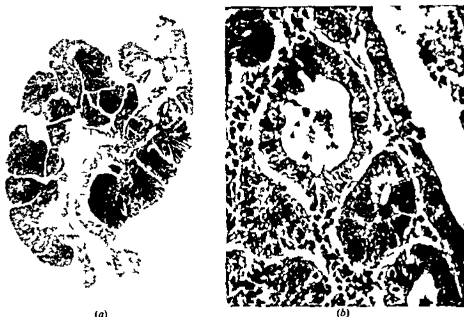



FIG 14 —(*a*) Adenomatous rectal polyp showing much irregular epithelial proliferation and patches of carcinoma *in situ* appearing dark in colour in this picture (*by courtesy of the Editor of* J R Coll Surg Edinb ) (*b*) patch of carcinoma *in situ* from one of the darker areas in (*a*) Though malignant in appearance these suspicious looking cells are still in their natural relationship to surrounding tissues

## PRE CANCEROUS NATURE OF BENIGN EPITHELIAL TUMOURS

The following points are evidence of the well-established close relationship between benign epithelial tumours of the intestine and cancer

(1) When patients with adenomas or villous papillomas of the rectum or both have been kept under observation over a period of years it has frequently been found that carcinoma has developed in a tumour previously known to be non malignant

(2) In the routine reporting on apparently benign tumours removed by local excision it is not uncommon to find unexpectedly a small focus of carcinoma in a tumour the greater part of which has the histology of an adenoma or villous papilloma Obviously the carcinoma has developed in a pre existing benign tumour

(3) Even in a large and typical carcinoma a careful search at the edge not infrequently reveals some remaining portions of a preceding benign tumour (Figs 18 and 19)

These facts justify the conclusion that an adenoma or papilloma of the colon or rectum should be regarded as a pre cancerous lesion This does not mean that all benign epithelial tumours inevitably become malignant or that carcinoma invariably begins in an adenoma or papilloma These lesions are described as pre cancerous only because clinical and pathological experience proves that cancer often develops within them

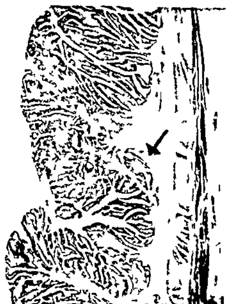


Fig 15 —Section through a large broad based papillary adenoma of the rectum showing a small focal carcinoma (marked by arrow)

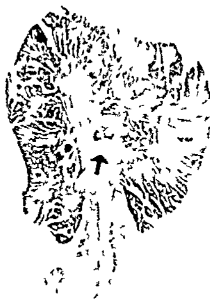


Fig 16 —Adenomatous rectal polyp showing much irregular epithelial proliferation (dark patches) and a small carcinoma commencing to invade the stalk of the tumour This invasive carcinoma is marked by an arrow (*By courtesy of the Editor of the* Lancet )

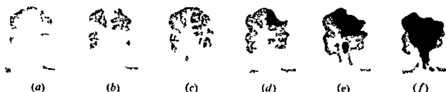



Fig 17 —Diagram illustrating stages in development of carcinoma in a pre-existing adenoma (*a*) Mucus secreting adenoma (*b*) proliferation in adenoma (*c*) carcinoma *in situ* (*d*) focal carcinoma (*e*) and (*f*) invasive carcinoma (*By courtesy of the Editor of the* Lancet )

## PRE CANCEROUS NATURE OF COLONIC POLYPOSIS

Colonic polyposis or familial intestinal polyposis is a hereditary disease characterized by the development within the colon and rectum of large numbers of adenomatous tumours It is a rare disease but during the last 30 years of research into its origin and treatment at St Mark s Hospital London more than 60





FIG 19 —Small protuberant carci noma of the rectum The central portion (marked by arrow) is in vasive but the growth on each side is benign

FIG 18 —Surface view of a large rectal tumour the upper third of which was hard and ulcerated and proved to be malignant (marked by arrow) The lower two thirds was soft and paler and had the histology of a villous papilloma

polyposis families (approximately 1 200 members) have been investigated and family pedigrees prepared The word member is used to describe polyposis patients their brothers and sisters and direct descendants of these individuals Amongst these members no fewer than 234 are known to have suffered from polyposis and 167 have developed intestinal cancer

**Familial characteristics**

Evidence that the disease is familial in character is not found in all cases of intestinal polyposis but when comparison is made between solitary and obviously familial cases no difference is noticeable in the size or the number or distribution of the tumours nor is there any difference in the age of onset symptoms or course of the disease The solitary cases of polyposis also tend to develop carcinoma after the same average period of 10–15 years and the average age of death from cancer is approximately the same for both solitary and obviously familial cases

**Onset and course of the disease**

The following facts concerning the inheritance of this disease are now well established Although inherited it does not usually manifest itself until childhood or early adult life the first symptoms being some looseness of bowel action accom panied by the passage of excess of mucus and perhaps small quantities of blood The course of the disease is very variable in different families and even in different members of the same family but in the more severe cases health is soon undermined and the patient becomes ill nourished and anaemic Cancer of the rectum or colon is almost certain to develop and it is not uncommon to find multiple foci or malig nancy when operation specimens are examined

Polyposis affects males and females equally and either may transmit the disease In most polyposis families only half the children are likely to inherit the abnor mality and so become capable of transmitting it to the next generation The

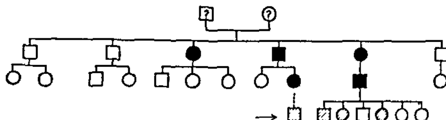


FIG 20 —Pedigree of a polyposis family Unaffected males and females are indicated by squares and circles respectively Members with both polyposis and cancer are marked black those with polyposis only are marked by shading Other illustrations of the member marked by an arrow are shown in Figs 21 and 22 (*Figs 20 21 and 22 by courtesy of the Editor of* Brit J Surg)

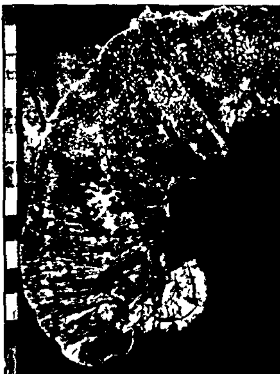


FIG 21 —Surface view of mucosa of the colon from a member of a polyposis family marked by an arrow in Fig 20 More than 5 000 tumours could be counted in this specimen None of them looked or felt like malignant tumours and this patient was successfully treated in the pre *malignant phase of polyposis*

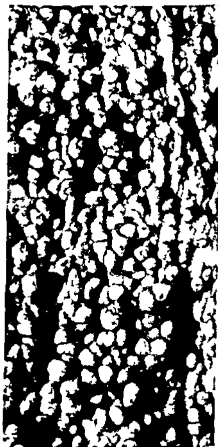


FIG 22 —Close up of surface of mucosa (*reproduced actual size*) *from patient* illustrated in Fig 21 and marked by arrow in Fig 20



Fig 23 —Small focus of epithelial proliferation in mucoas from a case of familial polyposis an early stage in the development of an adenoma



Fig 24 —Low power view of three adenomatous tumours from a case of familial polyposis Note normal mucosa between tumours (*By courtesy of the Editor of the* Lancet )

possibility of transmission by unaffected members is a question requiring further investigation but in the meantime it can be said that they are very unlikely to transmit the disease

The pedigree of a typical polyposis family is recorded in Fig 20 The patient indicated by an arrow developed symptoms of polyposis at the age of 16 years and was treated by colectomy and ileo rectal anastomosis 2 years later More than 5 000 tumours were found in the colon (Figs 21 and 22) The histology of another similar case of polyposis is shown in Figs 23 and 24

During recent years there has been a great improvement in the end results of the surgical treatment of colonic familial polyposis The main reason for this is because more and more patients are being treated in the pre malignant phase of the disease an advance made possible by follow up of both affected and unaffected members of polyposis families

## SEVERE LONG STANDING ULCERATIVE COLITIS

### Relation to cancer

Almost every surgeon who has inquired into the relationship between ulcerative colitis and cancer has reached the conclusion that severe ulcerative colitis pre

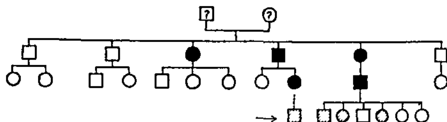


Fig 20 —Pedigree of a polyposis family Unaffected males and females are indicated by squares and circles respectively Members with both polyposis and cancer are marked black those with polyposis only are marked by shading Other illustrations of the member marked by an arrow are shown in Figs 21 and 22 (*Figs* 20 21 *and* 22 *by courtesy of the Editor of* Brit J Surg)

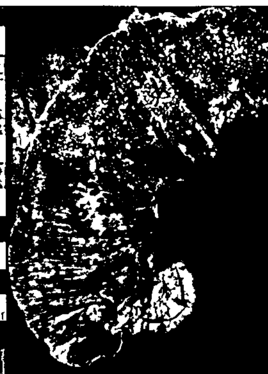


Fig 21 —Surface view of mucosa of the colon from a member of a polyposis family marked by an arrow in Fig 20 More than 5 000 tumours could be counted in this specimen None of them looked or felt like malignant tumours and this patient was successfully treated in the pre malignant phase of polyposis

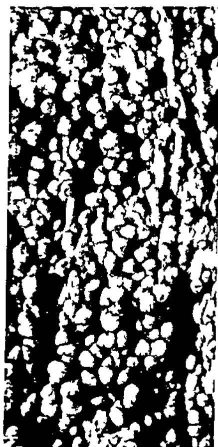


Fig 22 —Close up of surface of mucosa (reproduced actual size) from patient illustrated in Fig 21 and marked by arrow in Fig 20



FIG 23 —Small focus of epithelial proliferation in mucoas from a case of familial polyposis an early stage in the development of an adenoma

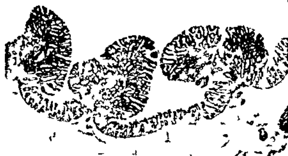


FIG 24 —Low power view of three adenomatous tumours from a case of familial polyposis Note normal mucosa between tumours (*By courtesy of the Editor of the* Lancet )

possibility of transmission by unaffected members is a question requiring further investigation but in the meantime it can be said that they are very unlikely to transmit the disease

The pedigree of a typical polyposis family is recorded in Fig 20 The patient indicated by an arrow developed symptoms of polyposis at the age of 16 years and was treated by colectomy and ileo rectal anastomosis 2 years later More than 5 000 tumours were found in the colon (Figs 21 and 22) The histology of another similar case of polyposis is shown in Figs 23 and 24

During recent years there has been a great improvement in the end results of the surgical treatment of colonic familial polyposis The main reason for this is because more and more patients are being treated in the pre malignant phase of the disease an advance made possible by follow up of both affected and unaffected *members of polyposis families*

## SEVERE LONG STANDING ULCERATIVE COLITIS

**Relation to cancer**

Almost every surgeon who has inquired into the relationship between ulcerative colitis and cancer has reached the conclusion that severe ulcerative colitis pre

disposes to carcinoma and that the extent of this predisposition has been under estimated in the past because of difficulties in diagnosis both clinical and patho logical Observations at St Mark s Hospital have confirmed this and also brought to light the fact that the incidence of cancer varies with the severity and duration of the preceding colitis Cancer is most likely to be found in severe cases of ulcera tive colitis which have continued for several years In cases personally studied the average duration of symptoms of ulcerative colitis before the onset of secondary intestinal cancer has been 15 years This latent period before the onset of malig nancy corresponds exactly to that observed in familial intestinal polyposis

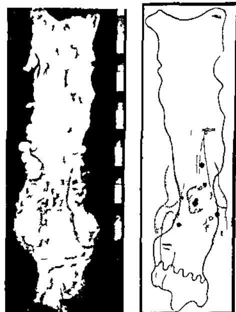


*Fig* 25 —*Rectal cancer following ulcer ative colitis* The growth had the appear ance of a dense stricture encircling the rectum It was anaplastic in character and had spread diffusely in the perirectal tissues and given rise to many lym phatic metastases (*By courtesy of the Editor of* Brit J Surg)



*Fig* 26 —*Small focus of colloid carcinoma* discovered within submucosa from a patient with ulcerative colitis treated by colectomy (*By courtesy of the Editor of* Ann R Coll Surg Engl)

In a consecutive series of 120 colectomies undertaken for the treatment of ulcerative colitis the author found unsuspected cancer in 7 cases (5 8 per cent) and these included many young people the average age of the 120 patients being 42 years No doubt in the future cancer will be found less frequently in colectomy specimens because surgeons are now operating at an earlier stage of the disease and before cancer has had time to develop

The present position may be summarized by saying that any patient in whom severe ulcerative colitis has lasted more than 10–15 years has entered a phase when intestinal cancer has become a definite risk



Fig 27 —Down growth of epithelium within an inflammatory polyp at the margin of a healing ulcer in a case of ulcerative colitis This must be distinguished from malignant invasion or infiltration



Fig 28 —Misplacement of normal epithelium within submucosa the result of reparative processes in the healing stage of ulcerative colitis

**Prognosis of cancer following ulcerative colitis**

When considering the prognosis of intestinal cancer following ulcerative colitis it is important to distinguish between patients diagnosed clinically as suffering from cancer and those in whom the presence of an unsuspected cancer was dis

covered in a colectomy which had been undertaken for the treatment of the colitis only

When clinical cancer follows ulcerative colitis it will generally be found that the growth is anaplastic in character and has given rise to widespread lymphatic metastases (Fig 25) On the other hand experience has shown that patients with a small focus of cancer in its pre clinical phase enjoy a good prognosis after colec tomy due to early removal of the malignant disease An example of a small microscopic focus of colloid carcinoma lying beneath intact mucosa—a chance finding in a colectomy specimen—is illustrated in Fig 26

## Recognition of malignancy

The recognition of minute foci of malignancy in operation specimens of colitis is not always easy In the sections they have to be distinguished from benign down growths of epithelium and islands of normal misplaced epithelium such as occur in the healing stage of ulcerative colitis as the result of reparative processes Two such cases are illustrated in Figs 27 and 28 This is an important point because it is in this healing stage of colitis that cancer is most likely to develop

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## III EXFOLIATIVE CYTOLOGY OF THE GASTRO INTESTINAL TRACT

HOWARD F RASKIN JOSEPH B KIRSNER AND WALTER L PALMER

## INTRODUCTION

THE fundamental characteristic of cancer cells which makes possible exfoliative cytology is loss of adherence to one another or to the parent tissue Coman (1944) demonstrated by micro manipulation that fewer milligrams of force are required to part carcinoma cells from one another than to separate normal cells Gastro intestinal cytology has developed more slowly than gynaecological or pulmonary cytology because of the greater difficulty in obtaining well preserved diagnostic exfoliated cells This handicap now has been largely eliminated by important technological advances The purpose of this chapter is to describe the simplest and most effective methods of collecting cells from various portions of the gastro intestinal tract to indicate the problems of the procedure and to evaluate its current usefulness

### Statistics

The Gastro intestinal Exfoliative Cytology Laboratory at the University of Chicago has been functioning for 5 years Table I lists the over all results for the 4 major areas of the alimentary canal

As the experience of the group increased and refinements in technique were achieved diagnostic accuracy increased Table II lists the results of the last 16 months

### Evaluation of cytological reports

The two most common causes of failure to obtain malignant cells are the submucosal location of the tumour without involvement of the mucosal surface and the presence of a thick tenacious exudate covering the surface of the lesion Errors may occur during the examination and interpretation of slides as atypical malignant cells are occasionally overlooked or unrecognized Failure to detect cancer when present is considered an error of omission a false negative report The converse of this situation is the misinterpretation or erroneous positive identification of non malignant cells a false positive report A report positive for malignancy may constitute cytological confirmation of disease already suspected or diagnosed by other means but clinically it contributes a decisiveness to the diagnosis not achieved by other methods In many instances the procedure has disclosed a neoplasm not demonstrated by other diagnostic tests Negative reports have a very considerable significance However diagnoses such as suspicious or suggestive of cancer are often misleading and confusing and contribute little to the evaluation of the clinical problem In the final analysis a positive or negative report must always be evaluated separately in each individual case

TABLE I

TABULATION OF EXAMINATIONS PERFORMED AND RESULTS FROM AUGUST 1951 TO AUGUST 1956

| | *Total cases* | *Clinically benign* | *Cytology negative* | *False positive* | *Accuracy of negative cases (per cent)* | *Clinically positive malignant* | *Cytology positive* | *False negative* | *Accuracy of positive cases (per cent)* |
|---|---|---|---|---|---|---|---|---|---|
| Oesophagus | 105 | 55 | 54 | 1 | 98 | 50 | 48 | 2 | 96 |
| Stomach | 975 | 778 | 768 | 10 | 98 | 197 | 167 | 30 | 84 |
| Pancreas and biliary system | 163 | 105 | 105 | 0 | 100 | 58 | 29 | 29 | 50 |
| Colon | 183 | 135 | 131 | 4 | 97 | 48 | 37 | 11 | 77 |

TABLE II

TABULATION OF EXAMINATIONS PERFORMED AND RESULTS FROM APRIL, 1955 TO AUGUST 1956

| | *Total cases* | *Clinically benign* | *Cytology negative* | *False positive* | *Accuracy of negative cases (per cent)* | *Clinically positive malignant* | *Cytology positive* | *False negative* | *Accuracy of positive cases (per cent)* |
|---|---|---|---|---|---|---|---|---|---|
| Oesophagus | 42 | 27 | 27 | 0 | 100 | 15 | 14 | 1 | 93 |
| Stomach | 388 | 306 | 304 | 2 | 99 | 82 | 78 | 4 | 95 |
| Pancreas and biliary system | 109 | 77 | 77 | 0 | 100 | 32 | 19 | 13 | 59 |
| Colon | 83 | 62 | 61 | 1 | 98 | 21 | 20 | 1 | 95 |

Every physician requesting exfoliative studies must appreciate that in spite of high standards errors due to failure to obtain cells *or to misinterpretation will* occur in a small percentage of cases Histological confirmation of cytologically diagnosed cancer should be obtained if possible to complete the study

## General technical principles

Experience has demonstrated that maximum efficiency is achieved when the same individual collects stains and reviews the slides (Graham 1954) A physician need not be involved in the more routine aspects of this time consuming and tedious work Skilled responsible technicians seem adequate for this purpose nevertheless a physician experienced in gastro intestinal cytology is essential to supervise and evaluate the results in relation to the total clinical situation

Successful exfoliative cytology requires continued meticulous attention to details Faulty or careless technique may result in the loss of the few malignant cells exfoliated in a particular case and hence a false negative report The cyto technician should know the clinical reason for the examination as well as the laboratory and roentgen findings Knowledge of the presence of an oesophageal diverticulum a large diaphragmatic hernia or subtotal gastric resection is impor tant when the stomach is to be intubated It is likewise important to know the site of a suspected lesion so that the Levin tube may be placed accurately and the suspected area lavaged vigorously Both the rubber and plastic tubes utilized are radio opaque facilitating fluoroscopy when necessary All tubes are passed through the mouth to avoid carrying nasal columnar mucosal cells into the stomach On two occasions knowledge that the patient had coryza prevented a false diagnosis of lymphoma of the stomach These patients had swallowed nasal secretions containing a large mononuclear cell resembling a lymphoblast two weeks after recovery from the upper respiratory infection re examination failed to produce similar cells Apart from the time spent with the patient collecting the material the technician usually devotes several hours in examining the slides hence clinical contact with the patient produces that extra endeavour by the technician on behalf of each patient during the tiring and laborious job of scanning *the slides* The average gastro intestinal slide requires half an hour of study compared to 5 minutes for gynaecological smears Usually 6 slides are prepared in the examina tion of the stomach while only 1 cervical smear is usually made These figures *alone will explain why gastro intestinal cytology will probably remain limited* to selected cases while mass cytological screening of the female population is possible for uterine cancers

The recognition of the typical cancer cell from any locality of the gastro intestinal tract is not difficult as a rule when sufficient cells are present The major problem has been the inconsistency of cellular quality and quantity Certain fundamental rules should be observed The examination should be deferred when detritus obscures the cellular component Patients with pyloric obstruction should be given a clear liquid diet for at least 1 day the stomach should be emptied and lavaged through a large Ewald tube the night preceding the examination Strictures of the colon require special efforts to ensure complete removal of faeces Food and barium interfere in two ways (1) the heavier contaminant will grind and pack the cellular material during centrifugation and (2) debris on the slide increases the difficulty of recognizing cancer cells

Certain precautions are necessary in the collection of the cytological material The aspirate should be placed promptly in 50 millilitre plastic centrifuge tubes suspended in an ice water bath This chilling is performed routinely for collections from all areas but is most important in the gastric wash to minimize enzymatic peptic digestion of cells Desquamated gastric columnar cells at room temperature for 10 minutes in the presence of strongly acid gastric juice often lose their cyto plasm and appear as naked degenerating nuclei The complete collection is centri fuged at 5 000 revolutions per minute for 2 minutes The supernatant fluid is decanted and the sediment from several tubes is rapidly transferred by spatula to a frosted glass slide A second slide is placed upon the face of the first the two slides are pressed together then pulled apart with a rapid horizontal motion and placed back to back in an equal mixture of 95 per cent alcohol and ether The slides should not be allowed to air dry in fact only a few seconds should elapse from the time the sediment is smeared until it is fixed

The purpose of this chapter is not to describe in detail the appearance of gastro intestinal cancer cells excellent photographs and descriptions are available in the monographs of the Staff of the Vincent Memorial Hospital (1950) and Papani colaou s atlas (1954) Moreover personal experience is more valuable than an atlas of photomicrographs Cancer cells are distinctive and are easily recognized they rarely simulate benign and atypical cells On the other hand several diseases may exfoliate non malignant cells mimicking cancer in many respects These cells have been encountered thus far in the oesophagus the stomach and the colon and have been responsible for false positive diagnoses An intriguing and potentially significant fact is that these atypical abnormal cells are the product of diseases generally thought to predispose to alimentary cancer namely oeso phagitis with leucoplakia benign healing gastric ulcer the post irradiated stomach pernicious anaemia in relapse (atrophic gastritis) and the regenerating phase of ulcerative colitis Exfoliative cytology thus provides an unusual opportunity to examine repeatedly gastro intestinal metaplasias and atypias

**Morphological changes**

Cowdry (1955) has described in great detail the differences in cytoplasm and nuclearplasm between benign and malignant cells Malignant cells are de differenti ated that is through a loss or failure to develop specific function the cells are not specialized They resemble one another more closely than the normal cell from which they originated More attention has been focused on the alteration of nucleo cytoplasmic ratio Many cancer cells exceed the size of normal columnar cells twofold or more The nucleus is disproportionately increased in size and indeed may constitute 80 per cent or more of the cell The intra nuclear material undergoes typical changes The nucleoli may increase in size and with the presence of false nucleoli and chromatin condensations the general appearance is one of irregular heavy clumping Such nuclear mottling is one of the more important features of the cancer cell Less common are changes in the nuclear membrane which may be thin and quite normal in appearance but more often are thickened with roughened edges Mitotic figures and abnormal cell division such as bi nucleated cells are noted occasionally The cytoplasm is usually reduced in amount and characteristically is irregularly vacuolated lacking smoothness and homogeneity Some cancer cells are phagocytic containing leucocytes and remnants of other

malignant cells within the cytoplasm Cancer cells scraped from malignant lesions immediately after surgery and stained with the Papanicolaou method resemble closely the exfoliated cells collected by simple lavage

## THE OESOPHAGUS

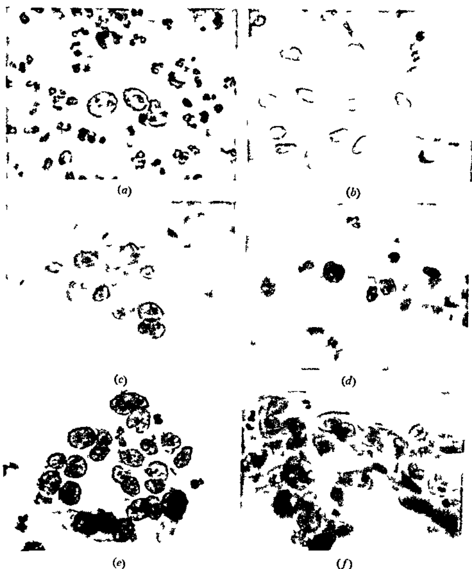
Exfoliative cytological examination of the oesophagus is the most direct and easiest of all the gastro intestinal cytological procedures and as a result the most accurate Only 2 false negatives and 1 false positive examination have been reported in 50 proven cases of cancer of the oesophagus examined in our laboratory Dysphagia the earliest symptom of carcinoma is the most common indication for the study Other indications are stricture secondary to chemical burns peptic ulceration and chronic inflammation Exfoliative cytology of the oesophagus is of value in cases of cardiospasm because of the increased incidence of carcinoma Klayman (1955) in a routine examination of a patient with cardiospasm detected malignant cells arising from a silent carcinoma infiltrating the dilated wall of the oesophagus Sideropenic dysphagia (Plummer Vinson syndrome) is another disease predisposed to the development of carcinoma The simplicity of the test makes it applicable as a clinical procedure there is no need for potentially dangerous instruments such as the mandril sound (Cabre and Garcia 1954) or the oesophageal bag (Lorber and Shay 1950) Routine yearly examinations of patients with oeso phageal diseases are useful and highly desirable

Exfoliative cytology is of value in the study of patients with post surgical recurrent carcinoma or with tumours at the cardio oesophageal junction an area from which positive biopsies are obtained with difficulty mechanical reasons such as kyphosis an unco operative patient or a cuff of normal tissue projecting above the lesion may render oesophagoscopy unsuccessful

**Technique**

The patient usually requires no sedation or topical pharyngeal anaesthesia Break fast is omitted but water is permitted up to 2 hours before the examination If obstruc tion is indicated by repeated vomiting or roentgen study residual mucus food and cellular debris are removed by gentle saline lavage This is rarely a problem except in severe cardiospasm when large amounts of thick tenacious fluid may require removal by vigorous Ewald aspiration Food barium and gelatinous exudate have been so firmly adherent to the oesophageal wall that several days of a clear liquid diet with daily aspirations have been necessary to cleanse the oesophagus completely A No 20 Levin tube is passed a distance of 45 centimetres the tip is then projecting into the cardia of the stomach Often in the presence of disease resistance will be encountered at a specific point in passage but usually the tube will advance rapidly to the cardia If the narrowing is severe the tube may double on itself and actually ascend the oesoph agus if inserted farther Such situations are best managed therefore under fluoroscopic control Rotation of the entire tube by twisting it at the gum margin will turn the tip sufficiently and permit it to engage the orifice of the stricture It is not absolutely necessary to pass the stricture but the yield of malignant cells will be higher and the absence of malignant cells will be more valid if the entire mucosal surface of the lesion has been irrigated With the catheter at a depth of 45 centimetres the patient is asked to swallow slowly approximately 100 millilitres of Ringer s or normal saline solution at the same time gentle aspiration is applied with a 100-millilitre syringe A general sampling of the entire oesophagus is thus obtained Twenty to forty millilitres of

## PLATE I



(*a*) Squamous cell carcinoma of the oesophagus (*b*) adenocarcinoma of the stomach (*c*) reticulum cell sarcoma (*d*) atypical gastric columnar cells from a benign gastric ulcer (*e*) bland gastric cells from a case of untreated pernicious anaemia (*f*) adenocarcinoma of the colon

[*To face page 81*

Ringer s solution are then injected through the Levin tube and immediately aspirated vigorously the volume of the return will vary but the collection of one half of the volume of each wash is satisfactory The tube is withdrawn systematically in 5-centimetre segments and several washes are made at each level Minimal narrowing of the oesophagus may often be located by the sudden increase in the amount of fluid recovered as an area of stasis dilatation and impaired oesophageal peristalsis has been reached The return volume can be increased by the Valsalva manoeuvre at the same time as the saline solution is introduced Another method to be tried when considerable amounts of wash escape into the stomach is to place the patient in a recumbent position with the head elevated Manipulation of the tube often produces some gagging and retching although of temporary discomfort to the patient these retroperistaltic contractions of the oesophagus definitely increase exfoliation and may regurgitate material of diagnostic value from below the area of narrowing An oesophageal wash is usually completed within 10 minutes

### Normal epithelial cells

The adult squamous epithelial cells of the oesophagus are similar to those of the mouth or uterine cervix These cells are large flat and many sided with orangophilic cytoplasm the nuclei are oval shaped centrally located slightly basophilic and contain finely granular chromatin Smaller round cells originating from the basal strata of the epithelium are seen less commonly These cells are not keratinized they have a deep blue green cytoplasm and a relatively large round hyperchromatic nucleus Pulmonary histiocytes polymorphonuclear leucocytes and a few lymphocytes complete the normal cytological picture A few columnar epithelial cells from the cardia or from the mucus secreting glands of the oesophagus are occasionally observed

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## PLATE I

*Erratum*

PLATE I (facing page 81)

Due to an error the illustrations have been printed in the wrong order

Would you please alter the lettering under each illustration to read as follows

| | |
|---|---|
| Instead of (a) | read (f) |
| (b) | (e) |
| (c) | (d) |
| (d) | (c) |
| (e) | (b) |
| (f) | (a) |

This will then conform to the key at the foot of the plate and the legends on page 81

ei are enlarged
g is moderately

h large nuclei
n
out are slightly
argement of the
odies Compare

ral enlargement
ndensations are
are quite similar

a patient with
alf times normal
e staining cyto

tion in nuclear
umping seen in
display of red

**Oesophageal cancer**

Malignant cells (Plate I (*a*)) from the oesophagus may take several forms Epidermoid cancers slough cells quite similar generally to the mature prototype however the malignant squamous cell is smaller This is the only exception so far encountered in gastro intestinal malignancy where the malignant cell is not larger than normal cells of the common epithelium The cytoplasm is frequently coarsely vacuolated and varies in colour from the basal green blue to the red orange of well developed keratinized pearls The determining factor of malignancy is the nucleus which is dark and dense with a heavy thick rough and irregular nuclear membrane best described as rat bitten Alteration of the nuclear cytoplasmic ratio may not be as outstanding as elsewhere in the digestive tract When the nucleus becomes unusually large the heavy clumping and hyperchromatism are less evident Bird s eye cells are phagocytic cancer cells with a clear zone of cytoplasm surrounding ingested particulate Tadpole cells are tumour cells consisting of large lobulated malignant nuclei enveloped by a thin zone of cyto plasm tapering off behind in streamer fashion Basal cell carcinoma may be identified by morphological similarities to cells previously described Frequently the exact type of cell present cannot be identified precisely and can be classified only as undifferentiated or anaplastic Adenocarcinoma of the oesophagus is uncommon but has been diagnosed several times These cells resemble adeno carcinoma cells of the stomach the cytoplasm is vacuolated and may contain secretory droplets of mucin These tumours are difficult to diagnose since they tend to extend submucosally with very little penetration of the squamous epithe lium hence not many cells exfoliate In one instance adenocarcinoma cells were identified pre operatively although the pathologist was unable to demonstrate the mucosal break through of submucosal tumour with serial sections (Raskin 1956) A case of fibre cell carcinoma of the oesophagus has been encountered the exfoliated cell is long and narrow with a hyperchromatic centrally placed nucleus Malignant melanoma of the oesophagus also exfoliates a characteristically recognizable cell

**Oesophagitis**

There is one hazard in the interpretation of oesophageal cells Johnson et al *(1955) and others who have studied the oesophagus extensively report* the occasional unavoidable misinterpretation of cells associated with inflammation as malignant These perplexing cells have been seen in peptic ulcer of the oesophagus and in oesophagitis with and without leucoplakia Fortunately relatively few cases of oesophagitis shed such cells many of which are too large to be squamous cancer cells Some approximate to small keratinized cells in size while others prob ably are giant tissue macrophages and yet other cells arise perhaps from mataplastic oesophageal glands Moreover these cells are few in number compared to the usually abundant exfoliation of typical malignant appearing cells from carcinoma These difficult cases are best managed by withholding a final report until after a period of appropriate therapy for oesophagitis Subsequent examinations will in all likelihood no longer demonstrate abnormal cells

Numerous giant squamous epithelial cells with relatively unchanged nuclear cytoplasmic ratios have been noted *in untreated pernicious anaemia (Graham*

and Rheault 1954) These macrocytic cells are truly spectacular several are capable of covering the entire field of the high power objective The cytoplasm and nuclearplasm are bland in appearance as if the normal quota of cell substance had been spread thin to fill an increased cell volume Occasionally multi nucleation and less commonly heavy nuclear clumping are featured These abnormal cells rapidly disappear within a few days after the administration of vitamin $B_1$ or folic acid Rubin (1956) has reported several cases of squamous macrocytosis in folic acid deficiencies of nutrition and pregnancy Gardner (1956) has noted similar cells in tropical sprue

## THE STOMACH

### Special apparatus

Exfoliative cytological studies of the stomach comprise 70 per cent of all gastro intestinal examinations at the Gastro intestinal Exfoliative Cytology Laboratory of the University of Chicago The indications are abnormalities demonstrable by roentgen studies or gastroscopy unexplained gastro intestinal bleeding pernicious anaemia recurrence of tumour following resection and a clinical suspicion of gastric cancer in the absence of any definite evidence The technique of obtaining gastric cells has passed through various stages Specialized apparatus using abrasive balloons (Panico et al 1950) and retractable rotatory brushes (Ayre and Oren 1953) have been only partially successful Experience with these instruments in a small number of patients indicated that the examinations were definitely un comfortable furthermore the cellular material was in no way superior to simple lavage Sheets of tissue several cell layers thick were in fact found more difficult to evaluate than individual cells The balloon may not scrape a small lesion as only a limited amount of the collapsed wall of the stomach can possibly be abraded by the roughened dilated balloon as it is pulled back and forth over the gastric mucosa Rossman and Wolf (1956) recently reported the accidental tearing of gastric mucosa with the Ayre brush on several occasions a small knuckle of mucosa caught in the telescoping brush was avulsed Since the over all accuracy does not compare with the simple lavage technique and the services of a physician are re quired abrasive methods have definite limitations and disadvantages

### Enzymes

Mucolytic agents such as papain and chymotrypsin have been used to remove the protective coat of mucus separating the underlying mucosa from the irrigating fluid Papain as advocated by Rosenthal and Traut (1951) produced satisfactory exfoliation in some cases but its action was unpredictable since columnar cells were occasionally digested together with mucus Considerable experience has been *accumulated in this laboratory with the use of chymotrypsin There is no scientific* proof of mucolytic action at *p*H 5 5 *in vivo* The stimulating studies by Rubin and Benditt (1955) and by Klayman et al (1955b) with chymotrypsin probably reflect the meticulous care and skill of these investigators in obtaining and interpreting the material more so than the use of a mucolytic agent Undoubtedly in time more productive methods of promoting cellular exfoliation will be developed but until then the simple lavage appears to be the most effective technique for gastric cytology

### Technique

In the presence of pyloric obstruction the stomach is lavaged with an Ewald tube the night before examination Less than 10 per cent of patients have retention but complete emptying of the stomach is an absolute prerequisite to a successful test The patient fasts for 8 hours A No 18 Levin rubber or plastic tube is passed through the mouth to the 60-centimetre mark The overnight gastric residual is placed in a 50 millilitre chilled centrifuge tube The stomach is then vigorously barbotaged with 300–500 millilitres of Ringer s or normal saline solution vigorous lavage of the stomach is highly essential The contents are aspirated repeatedly and re injected with a small amount of air to promote the greatest amount of turbulence in the stomach The position of the tube is constantly raised and lowered so that the force of the fluid being ejected will be dissi pated over the entire surface of the stomach The patient lies recumbent for part of the procedure so that the fluid may reach the cardia The irrigating fluid is aspirated after approximately 4–5 minutes of lavage This material is immediately centrifuged and smeared The purpose of the wash is primarily to remove protective strands of mucus and to weaken the surface cells of the tumour Five hundred millilitres of sodium acetate solution buffered to *p*H 5 5 are then instilled into the stomach The buffered acetate reduces gastric acidity and preserves cell morphology The patient lies for 2 minutes on his back and then rotates 90 degrees every 2 minutes The technician or the patient himself massages the upper abdomen during this interval In a thin person the fluid can be felt splashing about there is no discomfort After 8 minutes the patient sits up and the fluid is aspirated Quite often 450 of the original 500 millilitres can be recovered During the summer or if the patient is dehydrated 2 glasses of water may be permitted one hour before the examination to prevent rapid emptying of the stomach during the acetate lavage When the lavage fluid is difficult to locate it is most likely trapped temporarily in the stomach by gastric contractions By introducing 50 cubic centimetres of air through the tube the mucosa can be blown away from the tip allowing the water to seek the more dependent portions of the stomach Saliva should not be swallowed since this adds unnecessary material to the gastric wash The patient should be encouraged to retain the tube in the corner of the mouth to avoid excessive gagging and salivation Since it is impossible for a patient with a gastro-enterostomy or sub-total resection to retain all the fluid for 8 minutes he is allowed to remain on his back and left side and the volume of the lavage is reduced

### Gastric cytology

The stomach is undoubtedly the most spectacular of all organs of the digestive tract in its ability to exfoliate varied types of cells Normal gastric columnar cells are rectangular in shape with a faintly basophilic cytoplasm which may be vaculo lated and often indistinct The nucleus is unipolar when the cell is viewed from the side and centrally located when viewed end on The nuclearplasm is finely granular and may contain several small chromatin condensations Body and chief cells are not recognizable in over 1 000 stomachs examined by exfoliative cytology parietal cells have been noted on only two occasions apparently there is little exfoliation from the epithelium of the deeper portion of the glands in normal stomachs Goblet cells columnar cells with nuclei pushed to one side by a large mass of cytoplasmic mucin are not common they are encountered most frequently in atrophy or intestinalization of the gastric mucosa Other commonly observed cells are normal squamous epithelial cells from the mouth and the oesophagus and histocytes from the lung The latter cells are not troublesome diagnostically if dust particles are noted in the foamy cytoplasm The eccentrically placed nucleus

aids identification in addition these cells are often found trapped in long strands of mucus Many leucocytes and fewer lymphocytes are seen Clinical significance cannot be attached to the relative numbers of these mononuclears but a marked increase in normal lymphocytes may suggest the possibility of lymphoma

### Malignant cells

Adenocarcinoma cells (Plate I (*b*)) take many shapes and forms but always seem to resemble one another in each specific case The cells are always larger than *normal columnar cells a four fold increase in size is noted occasionally* Each malignant cell does not have all the morphological characteristics discussed earlier but the study of many cells will satisfy most of the requirements such as hyper chromatism changes in nuclear membrane vacuolization and so on On numerous occasions a most peculiar feature of gastric tumour exfoliation has been noted Quite often large old tumours both fungating and infiltrating yield a surprisingly small number of malignant cells while small relatively young tumours exfoliate abundantly There is no satisfactory explanation for this phenomenon other than the supposition that older tumours continually bathed by the gastric juices are denuded of friable surface cells and the more resistant core remains Smaller tumours are proliferating rapidly and thus shed cells easily increasing the possibility of obtaining malignant cells in early gastric cancers Seybolt et al (1951) have made similar observations

### Lymphoma

Gastric cytology is an excellent method of detecting lymphosarcoma of the stomach Klayman et al (1955a) have recovered lymphoblasts in 4 of 6 cases of gastric lymphosarcoma Even though there is frequently an increase in the number of normal lymphocytes the diagnosis of lymphoma cannot be made without identifying the lymphoblast While larger than a lymphocyte a lymphoblast is yet smaller than an adenocarcinoma cell and being rather scarce they may be completely overlooked A thin crescent of pale blue cytoplasm surrounding a round deeply basophilic nucleus with heavy chromatin particles characterizes the cell

Reticulum-cell sarcoma cells (Plate I (*c*)) are quite similar in general appearance *to the lymphoblast in fact there is good evidence that these are the stem cells for* many of the lymphomas Occasionally the distinction between reticulum-cell and lymphoblast can be made by minimal differences that is the reticulum cell is larger has coarser nuclear clumping and is more acidophilic The multi nucleated giant cell of the Dorothy Reed type has been recovered by several *investigators* from Hodgkin s lesions of the stomach On two occasions the authors have recovered benign giant cells with 10 or more nuclei from chronic antral ulcers in both instances an unusual granulomatous gastritis with multi nucleated giant cells in the ulcer base was demonstrated histologically

### Atypia

Between the extremes of definitely benign columnar cells and unequivocal malignant ones lies a veritable panorama of abnormal and atypical cells It has *been a painstaking at times fruitless* endeavour to determine the histological point of origin of the active or atypical cells found in gastric lavages when speci

mens have become available through biopsy or surgery Healing gastric ulcers have been the most consistent source of these cells Not all benign healing ulcers shed such cells but a sufficient number of cases have been encountered to make this phenomenon a definite entity in gastric cytology The morphology of these cells varies from simple enlargement of the total cell with minimal increase in nuclear clumping to cells (usually few in number) with many features of malignancy (Plate I (*d*)) Practically every cytologist who has studied stomach exfoliation extensively has at some time misinterpreted such cells With experience such errors should become extremely uncommon In some instances direct scraping of the ulcer base or edge yields cells similar to those seen in the wash haematoxylin and eosin stained tissue sections also have comparable cells It must be conceded that abnormal cells may originate from areas of gastritis often situated at some distance from the ulceration These bizarre cells disappear *on healing of the* chronic ulcer (or gastritis) acute ulcerations do not exfoliate such perplexing cells The most logical explanation seems to be that the epithelium attempting to cover the raw exposed area as rapidly as possible sends out streams of immature atypical cells often *only one cell layer thick The implication of this observation requires* serious thought Does carcinoma ever arise from benign ulcers and are these cells the forebears of the more misguided malignant ones? Morson s observation (1955) of intestinal metaplasia associated with benign and malignant conditions *from a pathological viewpoint complements the cytological impressions*

Other conditions occasionally associated with cellular atypia are unexplained cyclic vomiting hypertrophic gastritis prominent rugal folds and achlorhydria In a small series of cases the correlation between radiology gastroscopy gastric *analysis and biopsy (usually the Wood tube) has not been very informative The* abnormal cells disappear with clinical improvement in many cases which makes some of the complaints of the patients appear less functional

***Pernicious anaemia***

The gastric cytological changes associated with pernicious anaemia are of particular interest The stomach has long been implicated in the aetiology of this disease Two types of cells are desquamated by the atrophic mucosa Untreated patients and those in haematological relapse shed the bland P A cell *abundantly* This cellular stigmata of the disease can be found in the gastric wash of all patients in remission but may be few in number The diagnostic cell (Plate I (*e*)) is at least three times larger than the average normal columnar cell The cytoplasm and nuclear material are bland and delicate in appearance *The nucleus often has a* characteristic longitudinal crease The cell designated the active P A cell is smaller than the bland type and has many malignant features Caution should be exercised in diagnosing cancer in untreated pernicious anaemia particularly if only a few bizarre cells are observed *They may disappear after adequate therapy* Massey and Klayman (1955) found an occasional large bland columnar cell in some patients with simple achlorhydria gastric atrophy and carcinoma of the stomach

**Roentgen changes**

An interesting change also occurs in the cellular exfoliate of patients receiving small amounts of x ray to the gastric fundus for the treatment of peptic ulcer

Progressive increase in cell size and nuclear alterations develop soon after the tenth day of therapy and persist for 6 weeks The cytoplasm becomes clumped and vacuolated the nucleus may become pyknotic and hyperchromatic or it may increase in size with enlargement of nucleoli and chromatin granules The findings may suggest malignancy but careful scanning of the entire slide reveals that (1) the cytoplasmic nuclear ratio remains unchanged and (2) practically all the exfoliated cells are similarly affected whereas in carcinoma the cellular collection is a mixture of normal and abnormal cells

## THE PANCREAS BILE DUCTS AND DUODENUM

The diagnosis of cancer of the pancreas is one of the most challenging of gastroenterological problems Early experience with exfoliative cytology in this area was not encouraging Not only was intubation a difficult and unpredictable procedure for both the patient and the physician but errors of interpretation were frequent Lemon and Byrnes (1949) and McNeer and Ewing (1949) reported small series of carcinomas of the biliary tract correctly diagnosed by the cytological study of duodenal drainage Mackenzie and Miller (1949) recovered malignant cells from a rare primary duodenal carcinoma while Goldgraber et al (1953) reported a case of primary reticulosarcoma of the duodenum diagnosed by cytology

The availability of a safe and stable pancreatic stimulant secretin and the development of a rapid means of duodenal intubation in this laboratory encouraged further diagnostic efforts increasing the simplicity of the technique and the accuracy of diagnosis

The 60 per cent over all accuracy of correct diagnoses in proven cases of pan creatic bile duct gall bladder and primary duodenal carcinoma does not com pare with other regions but seems to be the best non surgical method of diagnosing primary malignancy in this segment of the digestive tract When the volume of pancreatic secretion following stimulation is small malignant cells may not be found as this usually indicates blockage of the pancreatic ducts and insufficient force of flow to wash out the cancer cells A tumour arising in the mid portion of the gland may progress and occlude the pancreatic ducts completely a long time before pancreatic insufficiency retroperitoneal pain or metastases produce the first symptoms of disease On the other hand jaundice is a fairly early symptom of cancer of the head of the pancreas and the ducts often remain partially patent in many cases at the time of intubation as bile is present in the drainage Cytological studies are almost always positive when the pancreatic tumour has penetrated the wall of the duodenum Exfoliative cytology theoretically should be an ideal method of diagnosis of cancer of the ampulla On several occasions malignant cells have been recovered from pancreatic drainage and duodenal washes which proved at surgery to originate in sites other than the pancreas The important function of cytology is merely to demonstrate the presence or absence of cancer statistically most of the cancers in this area of the digestive tract are pancreatic in origin Adenocarcinomas of the gall bladder and common bile ducts and an anaplastic primary tumour of the first part of the duodenum have exfoliated cells sufficient for a correct pre operative diagnosis of cancer

**Technique**

A *double lumen Diamond tube is used* the duodenal portion extends 6 inches beyond the gastric openings and has a small metal olive at its terminal end Separate drainage of the stomach and duodenal contents is obtained to prevent contamination of the duodenal aspirate by gastric juice and saliva The volume of duodenal juice and its bicarbonate content are measured for 30 minutes following administration of intra venous secretin

**A rapid method of intubation**

The patient is fasted and is given 160 milligrams of pentobarbitone sodium intra muscularly 30 minutes before intubation The Diamond tube is passed through the mouth until the 45-centimetre mark is reached the patient then lies on his left side on a low bench The head of the bench is raised on 18 inch blocks The patient then slowly swallows 12 centimetres (5 inches) of tubing This manoeuvre permits the metal olive and excess tubing to lie along the greater curvature of the body and fundus The patient then places his feet on the floor and while in a sitting position bends forward as far as possible and takes several deep breaths This position enables the anterior wall of the stomach to separate from the posterior wall and the metal olive to pass into the antrum The patient then lies on his right side his feet are now elevated 18 inches He lies for 5 minutes in the Trendelenburg position on the right side and then for 5 minutes on his back The position of the tube is checked fluoroscopically If the procedure has been performed correctly the metal bucket will be at the junction of the second and third portions of the duodenum The table is then placed in a horizontal position The stomach and duodenal tubes are connected to a suction pump and to a trap for collec tion of duodenal juice After several minutes the turbid duodenal fluid clears intra *venous secretin is given in a dose of 1 unit per kilogram The pancreatic flow* which may normally exceed 100 millilitres is collected for 30 minutes The sediment is utilized for cytological study and the supernatant fluid for chemical analysis Patients who are jaundiced are given inhalations of amyl nitrite to increase secretion The duodenum is then lavaged with saline solution in an effort to collect tumour cells from the mucosal surface The tip of the tube is then retracted into the stomach and any fluid present is collected for cytological examination The stomach is lavaged with saline solution because tumours of the body of the pancreas occasionally invade the posterior wall of the stomach by direct extension The complete examination often requires approxi mately 2 hours and is performed entirely by cyto technicians

The only cells recovered from a normal pancreatic drainage are columnar cells from the duodenal mucosa resembling those of the gastric mucosa During the height of pancreatic secretion the *p*H often reaches 8 0 which is sufficiently alkaline to produce fragmentation and pyknosis of cells A normal pancreas apparently does not exfoliate a recognizable cell The average positive drainage contains but a few malignant cells so that all atypical cells must be carefully scrutinized Some of the cells appear typically adenocarcinomatous others may be metaplastic and partially resemble squamous carcinoma

In several patients examined by the method described and in whom malignant cells were found the surgeon was unable to confirm the diagnosis the surgical opinion or biopsy report was usually interpreted as chronic pancreatitis but the subsequent clinical course or autopsy confirmed the diagnosis of cancer of the pancreas In spite of such dramatic cases the majority of biliary and pancreatic carcinomas have been *inoperable at the time of diagnosis* because of metastases

# THE COLON

The chief obstacle to satisfactory colonic cytology is the difficulty in cleansing the colon adequately Cancers of the colon readily exfoliate cells easily identified as malignant but the absence of faeces and barium is an absolute prerequisite to a successful test Colonic cytology has a very definite role in gastro enterology but offers no advantage for tumours within reach of the biopsy forceps Roentgenologists are highly accurate in the interpretation of colonic lesions but surgeons have found cytological study to be a valuable confirmative pre operative procedure Exfoliative cytology has been even more useful in patients with complaints suggestive of carcinoma but with normal radiographic and proctoscopic examinations malignant cells have been recovered in a few instances Repeat roentgenograms of the colon have then demonstrated a small lesion which was previously overlooked Other indications for exfoliative study of the colon include narrowed segments of bowel secondary to diverticulitis extrinsic masses or post surgical strictures recurrent carcinoma and unexplained melena Exfoliation of cells is more prolific from caecal and ascending colon neoplasms as these are polypoid and fungating lesions while those of the descending colon are stenosing and infiltrating Accuracy in the diagnosis of cancer of the colon regardless of site initially approximated 60 per cent but as better methods of colon preparation were developed the rate has increased so that presently 9 of every 10 carcinomas should be detected as reported in the studies of colonic cancer by Bader and Papanicolaou (1952) and Galambos and Klayman (1955)

### Technique

The procedure of cleansing the bowel is varied in the presence of partial large bowel obstruction When no obstruction is present the patients are given orally a cathartic dose of phosphate salts the evening prior to the test The patient is placed on a liquid diet 18 hours before the examination On the morning of the colonic wash he is given a series of normal saline enemas until the returns are absolutely free of faeces and barium To accomplish this the foot of the bed is raised on wooden blocks and the patient lies on his left side with the feet elevated In this position the enema fluid will run downhill to the transverse colon will not collect in the rectal ampulla and hence may be given slowly without cramping The patient then lies on his back and then on the right side permitting the cleansing fluid to reach the caecum After 10 minutes the enema is expelled On the average 5 enemas of 2 500–3 000 millilitres will completely cleanse the colon Much more difficulty is encountered in preparing the bowel in the presence of marked obstruction or ulcerative colitis In the former there is usually dilation of the colon with faecal impaction above the lesions and in such cases cathartics orally are contra indicated In ulcerative colitis faeces seem to adhere to the bowel and are removed only with difficulty furthermore patients cannot retain a large volume of fluid because of reduced calibre of the colon

To circumvent these problems the patient is placed on a liquid diet and given phosphate enemas and enemas of isotonic saline solution daily for several days if necessary Nevertheless patients occasionally cannot be cleaned completely because of the large quantity of stool above the lesion continually trickling down past the obstruction most of these strictures are on the left side and malignant cells may be recovered frequently as only the left colon requires lavage

The actual colonic wash is relatively simple The proctoscopic table is lowered a

standard proctoscope is introduced as far as possible without difficulty and an Ewald tube is passed through the proctoscope the latter is then removed One thousand cubic centimetres of normal saline are introduced into the rectosigmoid through the Ewald tube The fluid runs downward to the transverse colon The table is then raised to the horizontal position and readjusted to create a level surface The patient then lies on his right side and the fluid passes to the hepatic flexure when he lies on his back the solution reaches the caecum The tube is unclamped and the enema fluid recovered and filtered through a tea strainer The right side of the colon is higher than the poster iorly directed rectum enabling the enema fluid to drain in a few minutes A second identical wash is then performed there is less sediment and cells are more abundant Left sided lesions can be lavaged quite quickly by raising and lowering the table so as to shift the fluid about the descending colon

**Colonic cytology**

Small amounts of haemoglobin in the sediment are often significant as colonic cancers readily ooze blood The typical malignant cell resembles other adeno carcinoma cells but the red nucleoli are more prominent (Plate I (*f*)) The normal epithelium of the colon is composed of a relatively consistent type of simple columnar cell as it functions mainly to absorb water and to concentrate faeces mucus goblet cells are sometimes noted Compared to the complicated mucosa of the stomach there are no atypical or intermediate type cells except in ulcerative colitis Therefore with the exception of ulcerative colitis the presence of abnormal cells often indicates carcinoma Hyperplastic polyps including adenoma malignum rarely exfoliate an abnormal cell The studies in the literature describing abnormal cells in considerable numbers (particularly in ulcerative colitis) have utilized *abrasive balloons or scrapers and in a strict sense this is not exfoliative cytology* but more accurately a modified biopsy

**Ulcerative colitis**

The cytologist must be aware of the hazards of diagnosing carcinoma in ulcerative colitis Boddington and Truelove (1956) and Galambos et al (1956) have each studied this problem in 31 patients with ulcerative colitis This is the only disease of the bowel to our knowledge which can mimic carcinoma Other inflammatory conditions such as diverticulitis and post irradiation colitis have not exfoliated similar cells The examination of numerous patients with ulcerative colitis in various phases of activity indicates a consistent correlation between this phenom enon and the healing phase of the disease The atypia disappears or decreases when the disease subsides The cells are probably tissue macrophages and altered *cells originating in the crypts of Lieberkuhn* Therefore scrapings of the mucosa yield abnormal cells in greater quantity than simple lavage The cells range from large bland types similar in many respects to the bland P A cell of the stomach to distinctly malignant appearing cells Experience with this problem to date is limited but the safest policy to pursue in difficult cases seems to be as follows If the cells which appear malignant are few in number and are associated with cells manifesting lesser degrees of abnormality then one is most likely dealing with a regenerating mucosa On the other hand if malignant appearing cells are numerous and there are no diminishing degrees of metaplasia and if many of the nuclei contain *red nucleoli then a carcinoma should be strongly suspected* The absence of red nucleoli should not be an excluding factor but their presence is

ominous Truelove (1956) has noted conspicuous red nucleoli in ulcerative colitis but his material has been obtained by rectal scrapings

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# CHAPTER 6

# CARCINOID TUMOURS

## I CLINICAL ASPECTS

JAN WALDENSTROM

## INTRODUCTION

THE clinical picture characteristic of the special type of intestinal tumour that has been called argentaffinoma or carcinoid has been worked out slowly by a number of authors It had been already established that the cells constituting such tumours are argentaffine and chromaffine and it was therefore assumed that they were derived from cells with these staining properties which are found in the normal intestinal wall This cell type the Kultschitzky cell has been studied especially in man by the German pathologists Feyrter and Hamperl Masson and Berger (1923) had regarded them as forming a neurocrine organ and Feyrter (1953) gave them the name paracrine cells and described their normal occurrence in great detail The eminent Italian pharmacologist Erspamer (1954) investigated the same cell organ from a pharmacological point of view He conceived the idea of studying lower animals such as the octopus and the discoglossus where these cells are collected as separate organs and was thus able to extract a substance with marked pharmacological effects which he called enteramine Erspamer also gave the name enterochromaffine organ to the cells that produce enteramine and show chromaffinity (and argentaffinity) The chemical constitution was shown to be 5 hydroxy tryptamine and this substance has finally been synthesized

Until some years ago these tumours were regarded only as rare curiosities and it was commonly stated that a specific diagnosis could not be made before operation Investigations over the last 3 years have changed this picture completely we now know that carcinoid tumours with massive metastases may be the cause of a very typical but polysymptomatic syndrome of special interest to the gastroenterologist the cardiologist the dermatologist the allergist and also the nutritionist

## CLINICAL PICTURE

**Attacks**

The clinical syndrome is most readily diagnosed from the presence of vasomotor symptoms in the skin Sometimes there is a chronic cyanosis of the face with dilated vessels resembling the facies of polycythaemia In other rarer instances there are characteristic flushing spells which always start in the face and may then spread over the trunk and extremities The colour is often bright red but changes to pink and salmon red often occur quickly leaving blue lakes and white normal skin between them Coloured photographs of the flush (Plate II) were originally contained in the paper by Waldenstrom and Ljungberg (1955) The pattern fluctuates until the flush begins to fade first on the face and then on the body A short flush may last for only a few minutes flushes of longer than 10 minutes are rare One patient counted 24 flushes during 1 day but usually there are only 5–10 A severe

PLATE II



Functional circulatory influence from metastasizing carcinoid tumours
*(By courtesy of the Editor of Acta Medica Scandinavica.)*

flush is accompanied by palpitations and marked tachycardia sometimes a systolic murmur is heard over the heart during the maximal flush Borborygmus is often marked and the patient may experience colic and diarrhoea as signs of hyper peristalsis connected with a flush Psychic influences such as ward rounds may elicit a flush and these are regularly induced when the patient stands up Several patients have their severest flush in the morning when the bowels are opened others experience dyspnoea resembling asthma during a severe flush and several have been treated as asthmatics

These flushes tend to become more chronic as the disease progresses The facial hyperaemia may sometimes be marked, and some patients exhibit localized venectasies that have been called angioma planum (Portsma 1927) We have seen these phenomena in several of our patients

It is evident that the flushes are accompanied by very remarkable changes in the haemodynamics of these patients These phenomena have been studied especially by Thorson and the present author is quoting from the results of these studies Perhaps the most interesting objective change in the circulation is the occurrence of a completely different pattern of ballistocardiogram as soon as the flush starts the interpretation of such curves has always been regarded as difficult In these cases however the differences caused by external conditions may be reduced to a minimum as the same patient is always studied when lying still on the same table the only real change occurring inside the patient s own body Thorson is very cautious with the interpretations of his curves but it is obvious that the whole circulation and not only the blood vessels in the skin change during a flush Thorson s observation during a laparotomy in one patient confirmed that the peritoneal surface also shows flushing He studied in detail the variation in blood pressure heart murmurs and heart size radiologically and it is now established that a great many changes in the circulation accompany each flush Cardiac catheteriza tion was performed on one patient during a flush and it was found that the pressure in the pulmonary vessels increased markedly—a well known fact in animal experi ments where it has been shown that one of the effects of serotonine is to increase the intra arterial pressure in the lungs

## CARDIOLOGICAL PROBLEMS

The very interesting valvular heart disease found in cases with carcinoidosis has been described several times in single cases without even causing speculations regarding a causal connexion Observations by Cassidy (1933) where the patho logist made the diagnosis carcinoma by Scholte (1931) who saw the hyperaemia of the skin the intestinal tumour and the heart disease and by Millman (1943) who described the whole syndrome but stated explicitly that the patient suffered from two entirely unrelated conditions are quite illustrative It is remarkable that these early cases should have escaped the notice of later authors until Isler and Hedinger (1953) from the Pathological Institute in Zurich published three instances of widespread carcinoid tumours and right sided valvular heart disease At the same time Biorck et al (1952) observed one case with unusual cyanosis pulmonary stenosis and carcinoid tumour and mentioned another case with the combination (pulmonary stenosis and carcinoidosis) from Malmo Waldenstrom

and Ljungberg (1953) at the same time had analysed two cases with typical flushes and carcinoidosis During the following year the whole syndrome was worked out and its dependence on excessive formation of 5 hydroxytryptamine (5 HT) was made probable by the work of Pernow and Waldenstrom (1954) who demonstrated *the presence of increased amounts of this substance in the blood from 2 patients* Since these publications a large number of new observations have been made so that the total number of cases showing the complete syndrome with valvular heart disease or flushing or both now exceeds 40 20 coming from Sweden alone Regarding the localization of the valvular heart defects in these different patients I am quoting from the work of Thorson

Twenty two patients with valvular symptoms and carcinoidosis have been examined at autopsy In 1 case the tricuspid valve alone was found to be affected in 4 the pulmonary was the only localization in 11 the tricuspid and the pulmonary in 2 the tricuspid the pulmonary and the mitral valves and in 4 the valves of all the 4 ostia were pathologically changed

The valves usually show thickening and retraction sometimes even fusion of the valvular cusps and thickening of the chordae tendineae It is also quite common to find sclerotic thickening of the mural endocardium giving it a cartilaginous appear ance The changes are clearly illustrated in Figs 29 and 30 It is clear that both stenosis and incompetence might result from these changes The microscopical picture shows enormous increase in fibrous tissue with scattered fibroblasts Hedinger and Gloor (1954) pointed out that maximal increase in fibrous tissue was also observed in the pelvis in one of their cases as in the case reported by Cassidy (1930) *The possibility that hydroxytryptamine might stimulate the formation of* fibrous tissue must be borne in mind Surgeons are well aware of the fact that carcinoid tumours are often surrounded by fibrous adhesions

Thorson favours the hypothesis that the continuous pressure changes are the cause of the right sided valvular and endocardial thickening in the heart It is *impossible to prove this theory but it is at least an interesting point* A case has been observed of a female with marked flushings and a carcinoidosis that was proved at operation during the first period of observation there were no signs of valvular heart disease The heart roentgenogram was normal and only a faint systolic murmur was heard at the base or registered on the phonocardiogram During an observation period of about 2 years definite *signs of pulmonary valvular* disease appeared and a loud systolic murmur could now be heard over the base The diagnosis of pulmonary valvular heart disease was confirmed at necropsy an observation which seems to prove that the heart disease is secondary to the tumour and the flushing

The question arises as to whether there are any other similar processes known in cardiology Waldenstrom and Ljungberg (1955) have already discussed two very interesting analogies One is the endocardial fibro-elastosis that is practically found only in small children nearly always localized to the left side of the heart and some times of familial incidence This malady might be caused by an increased production of 5 HT in the mother s organism The substance would then exert its influence on the active left side of the child s heart and the malady thus be explained in the same way as the endocardial process in carcinoidosis Some data however are not in agreement with such an assumption

It has been shown that one twin may suffer from this type of heart disease whereas



FIG 29—Pulmonary cusps thickened and shrunken



FIG 30 —Tricuspid valves thickened

the other is free The humoral influence from the mother should be the same in both twins It is naturally also possible that these children have an excess production of 5 HT in their own bodies from congenital carcinoids or from hypertrophy of the 5 HT producing intestinal cells This problem should be investigated more closely with anatomical studies of the alimentary tract

Of still greater interest is the curious disease endomyocardial fibro-elastosis which occurs in African Negroes and also in a few whites who have resided for a long time in Africa Its pathogenesis is completely obscure and it does not seem possible as yet to find any plausible explanation Possible dietary influences may change the metabolism of tryptophan and 5 HT in such a way that there is a concentration of the latter

Over production of an endogenous metabolite having a strong pharmacological action seems of real importance in the genesis of valvular heart disease especially with congenital abnormality

**Metabolic problems**

Like most problems in internal medicine carcinoidosis is fundamentally a metabolic one It is interesting to see how the results of different biochemical investigations from all fields of biology may sometimes be applied to practical clinical questions as soon as our bits of knowledge find their place in the jigsaw puzzle The earlier pharmacological analysis of 5 HT activity at once explained the clinical findings in carcinoidosis Then the enzymatic studies on the degradation of tryptophan to 5 HT and the breakdown of this substance with the formation of 5 hydroxyindol acetic acid (5 HIAA) could immediately be applied to carcinoidosis Udenfriend et al (1955a and b) were able to extend the findings of 5 HT in the blood from patients with carcinoidosis (Pernow and Waldenstrom *1954*) by demonstrating its known metabolite 5 HIAA in large amounts in the urine from 1 patient with this disease These results have been amply confirmed and the last paper by Pernow and Waldenstrom (1956a and b) contains chemical and pharma cological analyses from over 30 Swedish cases with carcinoid tumours The material was divided into 2 groups (*a*) those patients where the operation on the tumour had probably been radical—among 11 such patients the amount of 5 HIAA found in the urine was usually normal or perhaps slightly elevated (*b*) the 23 cases where it is known that extensive masses of carcinoid tumour tissue are still present in the abdomen In most of these not only is the content of 5 HT in the blood very markedly augmented but there is also found a raised excretion of 5 HIAA in the urine Hanson and Serin have been able to follow the daily 24 hour output of 5 HIAA in 3 of our patients during their stay in the hospital Marked fluctuations were found but the values were always pathologically increased The diagnostic importance of this method is thus very great A positive find has always been cor roborated by operation and histological examination There are however a few histologically typical cases where the 5 HIAA values were normal

It may be appropriate now to comment on the chemical diagnostic procedures The urine from patients with carcinoidosis is usually of normal colour but may become quite red on standing This problem is at present being studied by Hanson who has pointed out that some indole substances are apt to form red compounds in urine probably by polymerization The well known urorosein reaction is indeed caused by indole acetic acid In 1 patient the red colour of the urine and the abdominal colics gave rise to a tentative diagnosis of acute porphyria

until the absence of porphobilinogen showed that this was erroneous With the addition of Ehrlich s so-called urobilinogen reagent—that is paradimethylamino benzaldehyde in hydrochloric acid—the colour of the mixture changes to a dirty blue after some time or quickly on boiling in the presence of 5 HIAA in large amounts This method may also be calculated as semi quantitative For a fuller discussion on this subject the reader is referred to Chapter 6 II by Pernow

By the aid of tracer studies it has been established that tryptophan is oxidized to oxytryptophan by a special oxidase A decarboxylase changes oxytryptophan to 5 HT and this is de aminized to 5 HIAA It is maintained by Udenfriend et al (1955a and b) that the decarboxylase necessary for the formation of 5 HT is highly

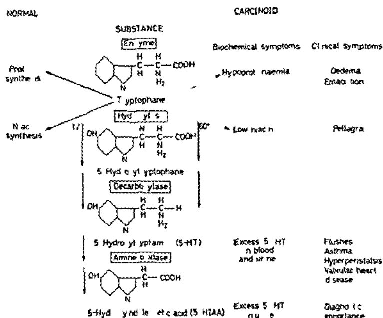



FIG 31 —Biochemical explanation of symptoms in carcinoidosis (modified from Udenfriend et al )

specific It is inhibited by isoniazid and needs pyridoxin and magnesium as co factors This enzyme is present in kidneys The interest in these substances has recently been stimulated as a result of a series of experiments that were interpreted as indicating that lysergic acid diamide (LSD) exerts its powerful action on the central nervous system as a 5 HT antagonist The neuropharmacology of 5 HT will not be discussed except to note that in the author s experience patients with carcinoidosis and high 5 HT content in the blood have never shown any remark able psychic disturbances It is possible that this may be explained by the fact that 5 HT occurs in the blood firmly bound to the platelets Ever since the first work when serotonine in the blood was identified as 5 HT this active principle in the plasma has been associated with the platelets Experiments by Toh (1954) seem to show that platelets take up 5 HT from its solutions and the same author has

given experimental data indicating that the normal 5 HT is formed in the intestinal wall and is transported in the blood bound to the platelets A high content of 5 HT in the blood from 1 case with carcinoidosis where a platelet free plasma fraction had a much lower content has been demonstrated (Pernow and Waldenstrom 1956a and b) These experiments are quite difficult technically and they should therefore be repeated with other patients It seems probable however that free 5 HT usually does not circulate in the blood and this may explain the fact that it does not pass into the central nervous system

One symptom that may be quite striking is a scaly brownish dermatosis usually situated on the arms and legs but also seen on the trunk (Biorck et al 1952)

One such case with severe dermatosis and a fiery red tongue has been treated with niacin The improvement was striking but it is naturally difficult to judge the therapeutic results from only 1 case

A convincing theoretical explanation of pellagra occurring in patients with carcinoid tumours has been given by Udenfriend et al (1955a and b) who points out that tryptophan is a normal precursor of both 5 HT and niacin It may well be supposed that a twenty fold increase in the production of 5 HT may cause a relative deficiency of tryptophan available for niacin formation In the author s patient the amounts of 5 HIAA found in the urine were quite high (70 milligrams in 24 hours) Confirmation of this hypothesis would prove a unique example of vitamin deficiency from metabolic causes The implications are possibly far reaching and it would be the first specific instance of deranged metabolism with a secondary deficiency state caused by enzymatic processes in tumour cells It seems probable that such competition between tumour cells and normal body cells will be found to explain many points in tumour cachexia

## PROGNOSIS

It is a well known fact that small carcinoid tumours often appear as multicentric lesions This is said to occur in about one third of all intestinal carcinoids and several patients have had 50–70 small nodules without metastases elsewhere It is thus possible that a systemic hypertrophy of the yellow cells may occur Another remarkable fact is the good expectation of life even in the presence of widespread metastases to liver and lymph glands Such patients have been described in the literature and some remarkable instances are to be found in the author s series One patient operated upon in 1943 had widespread hepatic metastases In 1956 her condition was practically unchanged except for more marked cardiac symptoms

It is thus obvious that the course of malignant carcinoid may be quite protracted and that cachexia is usually of late occurrence Many patients die from heart conditions but in some instances the tumour itself develops rapidly and the patient dies like a sufferer from any malignant tumour It is striking however that the toxic action of the 5 HT so often dominates the clinical picture Cases are also known where the intestinal tumour obviously causes defective intestinal absorption with secondary severe hypoproteinaemia 1 such case was described by Waldenstrom and Ljungberg (1955) The plasma protein was returned to normal after resection of the tumour It is possible that the hypoproteinaemia may have causes related to the tumour cellular metabolism

## TREATMENT

The only available therapy is surgery Most patients with resectable carcinoid tumours have abdominal symptoms of a completely unspecific nature and the diagnosis is made at operation We now have a number of personal observations where a definite diagnosis was made from the clinical picture together with the findings of 5 HIAA in increased amounts in the urine In these cases widespread metastases in lymph glands and liver are usually present and the operation will therefore not be radical The author recently observed and treated the case mentioned in the discussion on pellagra (p 98) where the syndrome was obviously more or less completely cured after a radical operation The patient a female aged 55 years suffered from flushing with a continuous cyanosis in the face and

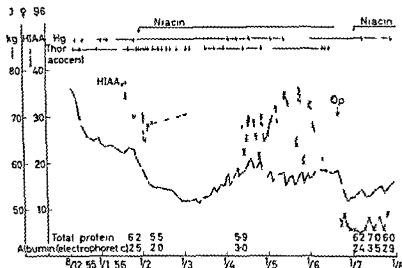



FIG 32 —Excretion values of 5 HIAA in ovarian tumour containing carcinoid tissue

attacks of diarrhoea The clinical diagnosis was confirmed by the finding of high HIAA values in the urine An abdominal mass obviously of pelvic origin was palpated On radiological examination the tumour was found to contain several teeth A tentative diagnosis of ovarian teratoma containing carcinoid tissue was made and at operation such a tumour was found but there were no visible or palpable metastases After extirpation of the tumour the clinical picture changed completely and the excretion of 5 HIAA became normal It is thus probable that a lasting cure has been obtained (Fig 32)

The possible importance of niacin in these patients has been discussed Clinical biochemistry does not offer any good measurement for the status of niacin saturation in the body It therefore seems advisable to give patients with severe carcinoidosis an extra supply of niacin It is possible that in future antimetabolites will become of importance Through the co operation of the Sandoz Company in

Basel Switzerland the author had an early opportunity to test the effect of the anti 5 HT substance BOL in our cases but without any definite effect Other antimetabolites might possibly have a favourable influence Heart failure is treated according to the usual principles

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## II CHEMICAL AND PHYSIOLOGICAL ASPECTS OF CARCINOID TUMOURS

BENGT PERNOW

IT was first suggested by Waldenström and Ljungberg (1953 1955) that the general symptoms associated with carcinoidosis might be due to increased secretion of 5 hydroxy tryptamine (enteramine serotonin) The isolation of this hormone had independently been carried out by two research groups Vialli and Erspamer (1933) isolated from intestinal mucosa a vasoconstrictor substance that stimulated smooth muscles and which they called enteramine in their opinion it was produced by the enterochromaffin cells of the bowel wall Erspamer and Asero (1952) subsequently identified enteramine as 5 hydroxytryptamine (5 HT) The same substance but called serotonin was isolated from blood serum and identified by Rapport et al (1948) It is a normal constituent of the platelets from which it is liberated during coagulation causing a local vasoconstriction 5 hydroxytryptamine has now been synthesized by several workers Exhaustive reviews of the relevant literature have recently been presented by Erspamer (1954a and b) and Page (1954)

### BIOSYNTHESIS AND METABOLISM OF 5 HT

Tryptophan as Udenfriend et al (1953) have shown is the mother substance in the synthesis of 5 HT in the organism The various phases of this synthesis are shown in Fig 31 on page 97 Tryptophan is first oxidized to 5 hydroxytryptophan under the influence of tryptophan oxidase which chiefly occurs in the liver and kidneys The 5 hydroxytryptophan is then decarboxylated to 5 HT by a specific decarboxylase that can be extracted mainly from the digestive tract

*In vivo* 5 HT is inactivated by an amine oxidase (Blaschko and Philpot 1953) The final product of this oxidative de amination is 5 hydroxyindolacetic acid (5 HIAA) a normal constituent of urine (Titus and Udenfriend 1954)

There is as was shown by Sjoerdsma et al (1956) a marked difference between the tryptophan metabolism in normal and in carcinoid patients This difference is shown schematically in Fig 31 on page 97

Under normal conditions the bulk of tryptophan in the food is utilized in building up protein and niacin only about 1 per cent is converted via 5 hydroxy tryptophan into 5 HT and similar substances In carcinoid this normal metabolism is completely disrupted about 60 per cent of the daily intake of tryptophan being metabolized to 5 HT This particular metabolism could take place therefore at the cost of protein and niacin production and in these patients it may give rise to deficiency symptoms consisting of anorexia and pellagra The disturbed tryptophan metabolism is reflected too in the urinary excretion of 5 HIAA Normally this is more or less constant even with major variations in the tryptophan content of the diet In carcinoid patients however it rises markedly with increased tryptophan intake

### METHODS FOR EXTRACTION AND BIOLOGICAL ASSAY OF 5 HT

Several useful methods have been reported for extraction of 5 HT from blood and urine Lembeck and Neuhold (1955) have employed a paper chromatographic

method for separating 5 HT from other substances Following chromatography 5 HT has been eluted from the paper and quantitatively assayed biologically The solubility of 5 HT in 95 per cent acetone has presented a further possibility of extraction and separation from other biologically active substances and from agents interfering with the biological assay The acetone method has also been the commonest one for extraction of 5 HT from carcinoid tissue

**Biological assay**

This is performed chiefly on isolated smooth muscle organs Erspamer has introduced the use of the isolated rat uterus In the oestrus phase that organ is highly responsive to 5 HT but virtually insensitive to histamine and acetylcholine Dalgliesh et al (1953) have shown that isolated rat colon is an excellent medium for quantitative assay of 5 HT Rat colon is practically insusceptible to histamine while the effect of acetylcholine has to be blocked with atropine Twarog and Page (1953) have used isolated heart from *Venus mercenaria* Administration of 5 HT in a very small dose increases the amplitude of the heart beats

**Chemical methods of 5-HT assay**

Chemical methods for determination of 5 HT in biological tissue have been devised *notably by Udenfriend et al (1955b) Three methods are serviceable* (1) determination of the absorption of 5 HT in ultra violet light (2) colorimetric determination with nitrosonaphthol as reagent (3) a fluorescence method enabling amounts of down to 0 05 microgram to be determined Jepson and Stevens (1953) determined quantitatively the fluorescence emitted by 5 HT in ultra violet light directly from the paper after chromatography reporting a sensitivity of 0 02 micrograms 5 HT

## 5 HIAA

Colorimetric methods for quantitative determination of 5 HIAA in urine have been elaborated by Erspamer (1955) Udenfriend et al (1955a) and Hanson and Serin (1955) among others In the method by Udenfriend et al $\alpha$ nitroso $\beta$ naphthol was used as reagent which is specific for 5 HIAA Hanson and Serin have used Ehrlich s aldehyde reagent which turns urine from patients with carcinoid blue This reaction is useful as a qualitative screen test in most cases of carcinoids but a simple method is also described for quantitative determination of 5 HIAA

**5 HT and 5-HIAA in blood urine, and tumour tissue from carcinoid cases**

The accompanying Table shows the normal values for 5 HT in blood and urine and for 5 HIAA in urine It includes too the corresponding values found in carcinoid patients collected from several investigators

The 5 HT content of the blood as will be seen is substantially elevated in patients with carcinoid tumours The highest value (6 5 micrograms per millilitre) has been reported by Pernow and Waldenstrom (1954) The bulk of 5 HT has been found in the thrombocytes while free 5 HT circulating in the plasma has shown exceedingly low values Goble et al (1955) found that the 5 HT content was substantially higher in blood from the vena cava and pulmonary artery than in

the arterial blood The 5-HT content of the peripheral blood might temporarily increase during attacks of flushing (Hegglin and Langemann 1955)

TABLE

FIGURES FOR 5-HT IN BLOOD AND URINE, AND OF 5-HIAA AND HISTAMINE IN URINE IN NORMAL PERSONS AND IN CARCINOID PATIENTS

| | *5 HT* | | *5 HIAA* | *Histamine* |
|---|---|---|---|---|
| | *Blood serum (μg/ml)* | *Urine (μg ml)* | *Urine (mg/24 hr)* | *Urine (μg/24 hr)* |
| Normal | 0 05–0 2 | 0 01–0 02 | 2–10 | 6–19 |
| Carcinoid | 0 25–6 5 | 0 10–20 | 15–1 680 | 15–7 500 |

The 5 HT content of urine like that of the blood shows great variations The values range from 0 1 to 20 micrograms per millilitre of urine the highest value being reported by Snow et al (1955) Pernow and Waldenström (1956) found elevated 5 HT values in 17 of 20 cases in which the hormone was assayed in blood and urine

Usually the urinary excretion of 5 HIAA is enormously elevated in carcinoid cases values of from 15 to 1 680 milligrams per day have been reported (Lembeck and Neuhold 1955) The urinary excretion of 5 HIAA appears to run parallel with the 5 HT content of the blood and urine Although physiologically greater interest attaches to a study of the biologically active substance determination of 5 HIAA is decidedly more practical as a routine method in suspected carcinoid or in follow ups It is simpler and requires less laboratory equipment Further 5 HIAA is far more stable and hence the values are more reliable The urinary output for 5 HT probably represents only a very small part of the total produced in the organism the bulk of it is absorbed by the tissues and broken down by amine oxidases Hence the excretion of 5-HIAA in the urine should be a more reliable criterion of the total 5 HT production Also other 5 HT metabolites than 5 HIAA however occur in the urine (Macfarlane et al 1956)

Large amounts of 5 HT can be extracted from carcinoid tissue as was first shown by Lembeck (1953) The reported values range from 15 to 2 500 micrograms 5 HT per gramme of fresh tissue The greatest amount has been found in primary tumours liver and lymph node metastases apparently contain smaller quantities Neither 5 HT nor 5 HIAA has been demonstrable in cerebrospinal fluid or faeces (Sjoerdsma et al 1956)

## URINARY EXCRETION OF HISTAMINE IN CARCINOIDS

It has recently been shown that carcinoid patients excrete not only 5 HT but also histamine in abnormally high amounts in the urine (Pernow and Waldenstrom 1956) The extraction method used was adsorption on an Amberlite ion exchange column and elution with hydrochloric acid The histamine was assayed on the isolated guinea pig ileum The amounts of free histamine found in urine was in 5 patients out of 7 higher than that normally found (*see* Table)

The fact that both 5 HT and histamine are found in increased amounts in the urine in carcinoid cases suggests a relationship of these substances in the body

Other observations speak in favour of this suggestion It has been shown that the distribution of 5 HT in the mucosa of the stomach is very similar to that of histamine (Douglas *et al* 1951) The presence of both histamine and 5 HT has been demonstrated in the mast cells (Benditt et al 1956a) Nothing is known how ever about the mechanism of release of histamine in these patients It might be assumed that the tumour cells produce both 5 HT and histamine It is also possible that the 5 HT secreted from the tumour cells acts as a histamine liberator in the body This would be in conformity with the observation by Feldberg and Smith (1953) that 5 HT has the ability to release histamine from living cells

## SYMPTOMS OF CARCINOID IN RELATION TO THE PHARMACOLOGICAL CHARACTERISTICS OF 5 HT

It now seems to be widely agreed that the general symptoms dominating the clinical picture of carcinoid are due to secretion of 5 HT from the tumour tissue for all of these symptoms can be experimentally duplicated by the infusion of 5 HT in human subjects or laboratory animals The symptoms are referable to three different organic systems

### Heart and circulation

The predominant circulatory symptoms are cutaneous vasomotor disturbances (flushing) tachycardia elevated pressure in the pulmonary circulation and right sided valvular lesions in the heart Flushing has been explained and experimentally demonstrated by Roddie et al (1955) who showed that infusion of 5 HT in the human brachial artery produced a deep flush in the ipsilateral forearm which within a few seconds became oedematous and assumed a cyanotic hue Con currently the volume of the forearm increased and the heat dissipation from the skin was reduced The functional basis of these symptoms is a pronounced con striction of the arteries and arterioles and dilatation of the capillaries and venules Cyanosis has also been observed after intravenous injection of 5 HT in man and after intraperitoneal administration in rats

The haemodynamic changes during flush have been studied in detail by Thorson (1956) Initially the cutaneous capillaries are dilated and the skin reddened and burning The cardiac sounds and ballistographic waves are for a few seconds diminished and then considerably increased Finally the reddening is succeeded by pronounced cyanosis and the heart sounds and ballistic amplitudes are again decreased These observations on carcinoid patients are similar to the results obtained by Roddie et al (1955) after 5 HT infusion

There has been a good deal of discussion regarding the cause of the valvular changes observed in the right heart in many patients with widespread carcinoidosis chiefly concerned with the relationship between these changes and the high 5 HT content of the blood Two mechanisms of origin are conceivable

(*a*) The valvular changes may be secondary to the increased pressure in the pulmonary circulation Direct recording of the blood pressure in the pulmonary artery has demonstrated a rise of blood pressure following infusion of 5 HT (MacCanon and Howath 1954) The changes in the tricuspid and pulmonary valves may therefore be regarded as hypertrophy compensating the elevated pres sure in the pulmonary circulation which however does not seem very likely

since similar changes are usually not demonstrable in cases with pulmonary hyper tension of other aetiology

Thorsen (1956) observed in some cases during flush a dilation of the right half of the heart and showed by intracardiac pressure tracings a transient tricupsid regur gitation This implies repeated stretching of the structures in the heart during the flushes repeated many times daily for a long time and might help to explain the late development of endocardial sclerotic lesions in some of these patients

(*b*) Another theory is that 5 HT directly stimulates the formation of connective tissue Changes in the right heart are chiefly observed in patients with liver metas tases In the series of 33 carcinoid cases reported by Pernow and Waldenström (1956) all patients with cardiac involvement had liver metastases except one remarkable case Since these metastases as well as the primary tumour continu ously secrete 5 HT the blood reaching the right heart has a high content of that substance Most of the 5 HT as already shown by Gaddum et al (1953) is broken down in passing through the lungs which contain an abundance of amine oxidase The blood reaching the left heart accordingly has a considerably lower content of 5 HT than the venous blood which is in conformity with the observation by Goble et al (1953) The stimulating effect of 5 HT on the formation of connective tissue was first suggested by Hedinger and Gloor (1954) this theory has been supported by experimental studies Thus Benditt et al (1956a) found that 5 HT is capable of producing hyperaemia and oedema when injected subcutaneously into rats Degranulation of the mast cells has also been observed after injection of 5 HT resulting in pronounced oedema and connective tissue formation (Asboe Hansen and Wegelius 1956)

Smooth muscle

*The respiratory organs*

Asthmatic attacks have been reported to accompany flushing in patients with carcinoid Moreover experimental studies have shown clearly that 5 HT affects bronchial tone Reid and Rand (1951) for instance observed broncho constriction in dogs after intravenous administration of 5 HT Similar observations have been made by Gaddum et al (1953) in cats and by Herxheimer (1953) in guinea pigs following inhalation of 5 HT

*The alimentary tract*

An apparently general complex in carcinoid patients consists of borborygmi diarrhoea and other signs of increased peristalsis together with the flushing 5 HT has very powerful stimulating effects on isolated segments of intestine and these have been studied specially by Erspamer (1940) In fact studies on isolated intestine of guinea pig or rat offer one of the most sensitive methods of assaying 5 HT The stimulating effect is also observed on the bowel *in situ* Even under deep anaesthesia 5 HT causes increased peristaltic sounds and evacuation of the gut (Page 1954) Borborygmi and abdominal pain can also be produced in man by intravenous administration of 5 HT (Spies and Stone 1952)

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## III PATHOLOGY OF CARCINOID TUMOURS

BASIL C MORSON

## INTRODUCTION

CARCINOIDS are epithelial tumours which arise from the Kultschitzky cells in the mucous membrane of the gastro intestinal tract They have the pathological features of very slow growing malignant tumours and patients may live for many years even in the presence of extensive secondary deposits There are how ever exceptions to this general rule

The term carcinoid was introduced by Oberndorfer in 1907 in order to dis tinguish this tumour from carcinoma Gosset and Masson (1914) and Masson (1928) showed that the tumour cells contained cytoplasmic granules which reduce silver salts This led to the use of the terms argentaffin carcinoma or argentaf finoma However the non committal term carcinoid is to be preferred for the affinity for silver is not specific to these cells Also there are tumours in the rectum called carcinoid which do not show argentaffin granules

In comparison with other forms of malignant disease of the gastro intestinal tract carcinoid tumours are uncommon They are however among the commonest malignant tumours of the small intestine and appendix Their importance has greatly increased since it was shown that they secrete 5 hydroxytryptamine or serotonin (Erspamer and Asero 1952) The presence of excessive quantities of this substance in the blood of patients with carcinoid tumours may produce a clinical syndrome whose most constant features are a peculiar type of flushing diarrhoea and right sided valvular disease of the heart (Biorck et al 1952 Thorson et al 1954) These discoveries have added to the interest and importance of a carcinoid which may now be regarded as an endocrine tumour

## GENERAL PATHOLOGY

### Origin

Gosset and Masson (1914) were the first to demonstrate that carcinoid tumours arose from special epithelial cells in the mucosa of the gastro intestinal tract One of the earliest accounts of the morphology of these cells was given by Kult schitzky (1897) and for this reason his name is very commonly used to describe them The Kultschitzky cells are most numerous in the mucous membrane of the duodenum (including Brunner s glands) followed by the small intestine (including Meckel s diverticulum) appendix colon and rectum In the stomach they are normally few in number but are increased in association with areas of intestinal metaplasia (Magnus 1937) They are also present in small numbers in the pancreas and gall bladder Masson (1928) has emphasized their entodermal origin An account of their distribution in animals has been given by Jacobsen (1939)

In the intestine the cells are situated mostly near the base of the crypts of Lieberkuhn not more than two or three being found in each crypt Occasionally cells may be seen nearer the surface of the mucosa The normal cell (Fig 33) is about the same size as its neighbours but it has a somewhat larger nucleus with a fine chromatin network and prominent nucleolus The cytoplasm contains fine

granules which always lie basal to to the nucleus and have never been observed to enter the lumen of the tubule In contrast the coarse granules seen in the neighbouring Paneth cells (Fig 33) lie in a supra nuclear position The Kultschitzky cell granules are eosinophil they reduce ammoniacal silver nitrate and give an intense yellow colour with bichromate solution The last two properties have led to the use of the terms argentaffin and enterochrome to describe these cells

Many attempts have been made to discover the exact chemical nature of the cytoplasmic granules in Kultschitzky cells and excellent accounts of these efforts are given by Jacobsen (1939) and Barter and Pearse (1955) As a result of work by



Fig 33 —Normal Kultschitzky cell Note the infranuclear granules The rather coarser supranuclear granules in a Paneth cell can be seen at the base of the tubule (Diazo method × 600 reduced by one quarter in reproduction)



Fig 34 —Carcinoid of the appendix The cytoplasmic granules are most dense around the periphery of the clump of tumour cells (Diazo method 100 reduced by one-quarter in reproduction )

Erspamer and his colleagues it is now certain that the granules are an artefact produced by the interaction of formaldehyde and 5 hydroxytryptamine or serotonin Confirmation of this work has come from a number of sources both chemical and pathological including that of Lembeck (1953) who first extracted 5 hydroxy tryptamine from a carcinoid tumour

## Sites

Carcinoids are most commonly found in the appendix and the small intestine usually the terminal ileum Less frequently they are found in the rectum (where they exhibit unusual and atypical features) in the colon the stomach (Martin and Atkins 1952) the duodenum and Meckel s diverticulum They have also been reported in the gall bladder (Porter and Whelan 1939) and in teratomas (Willis 1953) De Muylder and Fayt (1954) describe normal argentaffin cells and a carcinoid tumour in the lung The similarity of some bronchial adenomas to carcinoid was noted by Hamperl (1937) while Jarvi (1946) described tumours of the naso pharynx which contained numerous argentaffin granules Carcinoid tumours may arise at any site where normal Kultschitzky cells are found and this includes areas where ectopic gastric or intestinal epithelium is known to occur Ashworth and Wallace (1941) describe 28 cases in unusual locations

**Age and sex incidence**

Carcinoids have been reported at all ages from adolescence to extreme old age Cases of metastasizing carcinoid however are commoner in the older age groups In most of the larger series the sex incidence has been a little greater in men than in women in some there has been a preponderance of females This may be accounted for by the greater frequency with which appendicectomy is performed in women particularly in conjunction with pelvic operations It must be remembered that carcinoid is a remarkably silent tumour and is often an incidental finding at operations for other intra abdominal conditions

It is interesting to compare the age incidence of carcinoid tumours of the appendix and those in the small intestine which is really a comparison of those tumours which are rarely found to have any metastases at the time of operation and those in which lymphatic deposits are very commonly found A study of 22 cases of carcinoid of the appendix shows an age incidence of 16–67 years with a mean of 34 years—conforming with that reported for a larger series by Pearson and Fitzgerald (1949) On the other hand 14 cases of carcinoid of the ileo caecal region other than the appendix which have been studied by the author show an incidence of 35–82 years with a mean of 67 years Four of the patients were over the age of 80 years at the time of operation All except one of these cases had secondary deposits Pearson and Fitzgerald found a mean age of 66 years in their cases of metastasizing carcinoid and Dockerty and Ashburn (1943) a mean of 58 years The comparison between the age incidence of carcinoids of the appendix and small intestine supports the view that most of these tumours are very slow growing and that the development of metastases is a matter only of time

**Gross characteristics**

Carcinoids are usually small circumscribed tumours which tend to be sub mucosal in position and cause little ulceration of the overlying mucosa In cases of metastasizing carcinoid the lymphatic deposits are frequently larger than the primary growth The tumours are usually very hard and may appear yellow The colour is more obvious on the cut surface of the tumour and is due to the yellow colour of the cytoplasmic granules The fluorescence of the cut surface of a carcinoid tumour has been studied by Jacobsen (1939)

**Methods of spread**

Much local spread beyond the wall of the bowel is unusual although involve ment of the peritoneal coat is common Secondary peritoneal deposits may be found but these rarely lead to ascites

Spread to regional lymphatic glands occurs and is most commonly found in carcinoid of the small intestine Glandular involvement from carcinoid of the appendix is rare due to the early stage at which the diagnosis is made

Invasion of blood vessels in the neighbourhood of the primary tumour may be seen in histological sections Metastasis occurs primarily to the liver but also to lung heart kidney skin and other organs Because of the very slow rate of growth of carcinoid tumours removal of secondary deposits which are causing symptoms may be well worth while

## Histology

The typical carcinoid (Fig 34 and Plate III) consists of solid clumps or strands *of small closely packed cells* The tumour nuclei are very uniform in shape and size Mitoses are difficult to find The cells show a tendency to tubule or acinar formation and the larger clumps may be surrounded by a single row of cells which are columnar in shape and give the appearance of palisading as in basal cell carcinoma of the skin The cytoplasmic granules typical of carcinoid are most dense around the periphery of the clumps of tumour cells (Fig 34) When a layer of palisade cells is present their granules are found in an infra nuclear position as in the normal Kultschitzky cell The tumour cells infiltrate surrounding tissues particularly nerve sheaths and may be seen within the lumina of lymphatics and blood vessels Varying degrees of anaplasia do occur but are uncommon These are the histological characteristics of the great majority of carcinoid tumours but particularly those in the appendix and small intestine Carcinoid tumours of the rectum have atypical features which will be described later

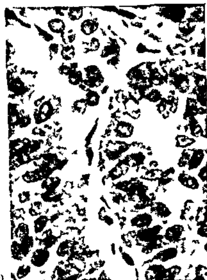
Histologists have noted an excessive amount of smooth muscle in and around carcinoid tumours This could be the result of long standing interference with local muscular contractions—a work hypertrophy On the other hand it is possible that the excessive secretion of 5 hydroxytryptamine by the tumour cells may cause a local hyperplasia of smooth muscle

*The histological diagnosis of carcinoid despite the introduction of biochemical* tests remains of primary importance It has been customary in the past to rely on the morphological appearances in an ordinary haematoxylin and eosin section without any attempt to demonstrate the specific cytoplasmic granules It is true that these granules are strongly eosinophilic in freshly fixed tissue (Plate III (*a*)) but this is a non specific reaction and may be mimicked by other intestinal tumours It is important to confirm the diagnosis of carcinoid by using one of the more specific staining techniques

The property of reducing ammoniacal silver to metallic silver (argentaffin reaction) *is the one most commonly used for confirming the diagnosis* of carcinoid in routine histological laboratories (Plate III (*b*)) This reaction cannot be regarded as very specific for the granules are not distinguished from either melanin or lipofuchsin All the different modifications of the argentaffin reaction are slow and difficult and are seldom successful unless performed by a skilled technician Precipitation tends to occur during the preparation of the section which not only obscures the tissue under examination but may give rise to artefacts On the other hand the Diazo method (Clayden 1955) which stains the granules rust red (Plate III (*c*)) is quick simple and reliable and may be successfully performed by a relatively inexperienced technician The section remains clean and the granules are clearly stained

Because the granules seen in carcinoid tumours are an artefact produced by the interaction of formalin and 5 hydroxytryptamine they can be demonstrated only in material which has been fixed in formol saline Fixatives containing chromates *are unsuitable* The granules gradually disappear from unfixed tissue and can seldom be demonstrated at all in necropsy material The longer fixation is delayed after surgical removal or biopsy the poorer will be the results Moreover it may be seen that the staining of the granules at the periphery of a carcinoid tumour is

## PLATE III

(a)   (b)

(c)   (d)

(*a*) Carcinoid granules are eosinophil (haematoxylin and eosin × 600)

(*b*) The granules are stained black by silver impregnation methods (× 600)

(*c*) The granules are stained rust red by the Diazo method (× 600)

(*d*) Carcinoid of appendix with anaplastic features The cytoplasmic granules are stained rust red by the Diazo method (× 450)

better than at its centre This is explained by the more efficient fixation of the tissue where it is most closely in contact with the formalin Jacobsen (1939) has pointed out the importance of the temperature factor He found that if fixation is delayed for 6 hours at 37 C this was sufficient to destroy the granules in normal Kultschitzky cells

**Cardiac changes in metastasizing carcinoid**

Thorson et al (1954) described cardiac changes in patients with metastasizing carcinoid A detailed account of the pathological findings in the heart has been given by Goble et al (1956) There may be stenosis of both the tricuspid and pulmonary valves and hypertrophy of the right ventricle Histologically there is no significant difference between these lesions and those found in chronic rheumatism their pathogenesis is obscure

## REGIONAL PATHOLOGY AND PROGNOSIS

**Tumours of the appendix**

These are usually very small circumscribed tumours seldom more than 1 centimetre in diameter Most are situated nearer the tip than the base of the organ Others show a more diffuse involvement of the appendix and the diagnosis in these cases is unsuspected until microscopic examination Of 22 cases within the author s experience 3 were associated with mucocele due to blockage of the lumen of the appendix A few were found incidentally at operations for other intra abdominal conditions but most of the examples of carcinoid of the appendix in this series were removed because of associated acute or chronic appendicitis

The histological appearances and behaviour of the great majority of carcinoids of the appendix are those of a very slow growing malignant tumour There is no justification for the use of the term benign carcinoid which is often applied to the small non metastasizing carcinoids of the appendix except as an indication of their almost invariably good prognosis after surgical removal Of 22 cases of carcinoid of the appendix studied by the author and followed up for periods of 2–22 years only 1 recurred The patient a female aged 20 years died within a year of appendicectomy from metastases in the liver and lungs There was evidence that the tumour had assumed more malignant histological characteristics than is usual The cells showed variation in shape and size of nuclei with an increased number of mitoses and diminution in the amount of cytoplasmic granularity (Plate III (*d*)) Although metastasizing carcinoid of the appendix is rare, it may occur even with a conventional histological pattern Stewart and Taylor (1926) reported a carcinoid of the appendix with large pelvic peritoneal deposits Removal of these together with the primary tumour effected a cure and the patient was alive and well 10 years later These authors collected 8 other cases of metastasizing carcinoid of the appendix from the literature Hopping et al (1942) reported a total of 16 cases from the literature and added a case of their own in which extensive intra abdominal deposits occurred including involvement of the right ovary

**Small intestine and caecum**

Most carcinoids of the small intestine and caecum are found in the region of the terminal ileum and the ileo caecal junction Whereas tumours of the appendix

are nearly always single those in the small intestine are frequently multiple Dockerty and Ashburn (1943) state that the tumours are multiple in 30–50 per cent of cases the number varying from 2 to 68 in one of their cases This is important in surgical treatment for a radical resection of a segment of ileum for a macro scopically obvious tumour may leave behind smaller tumours which can be discovered only by careful palpation of the remaining bowel

The tumours are mainly submucous in position and vary in size from that of a pea to a plum They may cause stenosis with dilatation and hypertrophy of the wall of the bowel proximal to the growth Kinking of the intestine and intus susception may also occur Much local spread beyond the wall of the bowel is unusual

By the time of diagnosis most cases of intestinal carcinoid have developed metastases particularly in the regional lymphatic glands One reason for the late diagnosis is the small primary tumour within the relatively large lumen of the intestine which fails to give rise to any obstructive symptoms This also explains why carcinoid of the small intestine is often an incidental finding at operation for other intra abdominal conditions

Despite the latent behaviour of intestinal carcinoid the prognosis is usually good Dockerty and Ashburn (1943) state that the natural history of carcinoid tumours is one of slow evolution with a long pre operative phase and post operative survival Terplan et al (1940) have reported a case of survival for 5½ years in the presence of the primary growth lymphatic and hepatic metastases The patient died from drowning and at post mortem examination the metastases had not increased appreciably in size That metastatic deposits of carcinoid may remain stationary in size over a period of many years is illustrated by Case 1 in the accompanying table This patient is alive and well 8 years after laparotomy and clinically her secondary deposits have not increased in size during this period The slow rate of growth of carcinoid tumours of the ileo caecal region is a reflection of their histology These appearances have been described earlier in this chapter They are those of a malignant tumour of a very low grade of malignancy This is the main reason for the survival of patients with widespread metastases it also accounts for the results of surgical treatment which are invariably good this is well shown in the cases reported by Stewart and Taylor (1926) Cameron (1938) Mallory (1940) and Dockerty and Ashburn (1943)

In the table on page 113 there are clinical and pathological details of 8 patients with metastasizing carcinoid of the ileo caecal region (excluding the appendix) who have been followed up after radical or palliative surgical treatment They have recently had urine tests for 5 hydroxyindoleacetic acid (5 HIAA) in order to detect or confirm the presence of metastatic deposits of carcinoid The tests have been performed by Dr J B Jepson of the Courtauld Institute of Biochemistry at the Middlesex Hospital London using his paper chromatographic method (Jepson 1955) for both qualitative and quantitative determinations A further 5 cases taken from the records of St Mark s Hospital London show 1 post operative death due to pulmonary embolus 2 deaths from an associated carcinoma of the colon and 1 death from old age 13 years after operation The clinical record of the fifth case suggests that the patient died from extensive liver deposits of carcinoid which were known to have been present for at least 7 years prior to death

The cases in the table can be divided into two groups First those patients who

TABLE

CARCINOID OF ILEO CAECAL REGION (EXCLUDING THE APPENDIX)

| | *Age* | *Sex* | *Site* | *Metastases* | *Operation* | *Result* | *Urinary 5 HIAA in μg/ml* |
|---|---|---|---|---|---|---|---|
| 1 | 52 | F | Ileo-caecal valve | Peritoneum pelvis liver | Ileo transverse colostomy | Well 8 years | 60–80 |
| 2 | 81 | M | Ileum | Glands peritoneum | Ileo transverse colostomy | Well 2 years | 20–50 |
| 3 | 8[illegible] | F | Ileum | Glands (inoperable) | Resection of primary and ileo transverse colostomy | Well 12 months | 50–100 |
| 4 | 7[illegible] | M | Ileum | Glands | Radical resection | Well 5 years | 0–40 |
| 5 | 35 | F | Caecum | Glands | Right hemicolectomy | Well 5 years | 20–30 |
| 6 | 80 | F | Ileum | Glands | Radical resection | Well 4 years | Normal |
| 7 | 82 | F | Ileo-caecal valve | Glands | Right hemicolectomy | Well 8 months | Normal |
| 8 | 55 | F | Ileum | Glands | Right hemicolectomy | Well 8 months | Normal |

Normal level = 0–10 μg/ml

were found at laparotomy to have inoperable deposits of carcinoid and yet have remained alive and well Secondly those cases who remain alive and well after radical removal of the primary growth and all known metastases None of the cases with a raised level of urinary 5 HIAA show any of the humoral manifestations of metastasizing carcinoid On the contrary the patients in the first group (cases 1 2 and 3) who are known to have inoperable deposits of carcinoid are remarkably well despite their advanced age Macfarlane et al (1956) have stressed the inconstancy of the relationship between the clinical picture the pathological distribution of the tumour tissue and the level of 5 HIAA in the urine

The second group (cases 4–8) illustrates the value of quantitative estimations of urinary 5 HIAA in the detection of post operative recurrence Three of these patients have normal levels of 5 HIAA or none at all suggesting that they are free of recurrence On the other hand patients 4 and 5 have abnormal levels of urinary 5 HIAA and it may be presumed that they still harbour deposits of carcinoid In both these cases there was involvement of lymphatic glands in the surgical specimen In case 4 these were present near the point of ligature of the regional blood vessels

Some consideration must be given to the procedure to be adopted in a case of recurrence due to carcinoid as detected by a urine estimation of 5 HIAA Bearing in mind the very slow growth of these tumours and that patients may remain alive and well for many years even in the presence of metastases no active treatment or surgical intervention would appear to be necessary unless the level of

5 HIAA rises or the patient develops humoral manifestations In either case the surgical removal of as much tumour as possible might be considered

**Carcinoid of the rectum**

An increasing number of cases of carcinoid of the rectum are being reported particularly in the American literature These cases show histological appearances which are atypical when compared with carcinoid of the ileo caecal region and their origin from true Kultschitzky cells is open to doubt Only 21 cases of carcinoid of the rectum have been seen at St Mark s Hospital over a period of 25 years 12 of these were in males and 9 in females Their ages varied from 24 to 68 years with a mean age of 44 All but 1 of these tumours presented as small *submucosal nodules about 1 centimetre in diameter They were found accidentally* either in operation specimens removed for adenocarcinoma of the rectum (5 cases) or during rectal investigation of anal symptoms due to a variety of causes including haemorrhoids (15 cases) They were usually thought to be simple adenomas All but 1 of these 15 cases were treated by local excision none has recurred or developed metastases One case was treated by a radical operation but no secondary deposits were found and the patient remains alive and well Jackman (1954) states that local excision is adequate treatment for the small submucosal variety of rectal carcinoid

It would appear that only a small percentage of cases of rectal carcinoid develop metastases Horn (1949) found 5 cases of metastasizing carcinoid in a series of 56 cases taken from the literature More recently Jackman (1954) has referred to 9 cases in a series of 44 tumours In the St Mark s Hospital series only 1 case was clinically and pathologically malignant This presented as a large ulcerating tumour of the upper third of the rectum Biopsy showed a degree of anaplasia not usually found in carcinoid tumours and a radical operation was therefore performed Secondary deposits were found in the liver and the operation specimen contained lymphatic metastases This case has been reported in detail elsewhere (Gabriel and Morson 1956) A study of metastasizing carcinoid of the rectum reported in the *literature suggests that the size of the tumour the presence of surface ulceration* and fixation to surrounding tissues are the main factors to be considered in any assessment of the degree of malignancy Biopsy of a lesion suspected clinically of being malignant will probably reveal histological evidence of anaplasia not usually seen in the small submucosal type of rectal carcinoid

A study of the St Mark s Hospital series showed that there are 3 histological types of rectal carcinoid (1) the type which has the histological appearances of carcinoid of the ileo caecal region and shows the typical cytoplasmic granules after treatment with the silver impregnation and Diazo techniques—these tumours may be called true carcinoids (2) the atypical carcinoid of the rectum which does not show granules and has a distinctive histological appearance of its own and (3) the tumours with some of the histological appearances of both these types but in which only a minority of the tumour cells show cytoplasmic granules

Five out of *the 21 cases in the St Mark s Hospital series were true carcinoids* They presented as small submucosal nodules and were histologically identical with carcinoid of the ileo caecal type Fourteen cases showed the appearances of the atypical form of rectal carcinoid Treatment with the silver impregnation and Diazo techniques failed to reveal any cytoplasmic granules These cases had a

distinctive histological appearance (Fig 35) the cells were small very regular in shape and size, and mitoses were difficult to find They formed solid clumps which resembled those seen in ileo caecal carcinoid but most of the tumour cells were arranged in an adenomatous pattern Some of the cases showed ribbon like festoons of columnar and prismatic cells as described by Stout (1942)

*In recent years many such tumours both clinically benign and malignant* have been reported in the American literature Lastly there were 2 tumours which had some of the histological appearances of both the true and the atypical forms



FIG 35 —Carcinoid of the rectum Much of the tumour resembles the ileo-caecal type of carcinoid but in the lower part of the illustration the cells are arranged in an adenomatous pattern (Haematoxylin and eosin × 100 reduced by one third in reproduction )

of rectal carcinoid but in which only a minority of the tumour cells showed cytoplasmic granules The first of these cases presented as a small submucosal nodule Tubule formation was more pronounced than is usually seen in ileo caecal carcinoid and granules were present in only a very few of the tumour cells The *second case was the metastasizing carcinoid of the rectum reported elsewhere* (Gabriel and Morson 1956) and referred to earlier Histological examination of this tumour revealed granules typical of ileo caecal carcinoid in a minority of the malignant cells Further there was a tendency to tubule formation in some areas with the secretion of small amounts of mucus Other parts of the tumour showed clumps and ribbons of cells which resembled the appearances of the atypical form of rectal carcinoid

The histology of these two cases suggests that the true and atypical forms

of rectal carcinoid are closely related and that transitional forms may occur Rigdon and Fletcher (1946) reported a case of multiple carcinoids of the rectum which showed an atypical histological picture but cytoplasmic granules were present in some of the tumour cells

The histology of the atypical form of rectal carcinoid and the absence of cyto plasmic granules suggests that their histogenesis is different from the conventional or true type of carcinoid tumour Three types of cell may be found at the base of the crypts of Lieberkühn in the rectal mucosa First there are Kultschitzky cells with their infranuclear granules Secondly Paneth cells may be seen but these are often absent Thirdly there are low columnar cells which are non granular and usually non secretory although occasionally small droplets of mucus may be seen in their cytoplasm The presence of these droplets indicates that some of these simple columnar cells may develop into mature goblet cells

The origin of the true type of carcinoid from the Kultschitzky cells cannot be disputed Tumours of Paneth cells have never been described It is suggested that the group of atypical rectal carcinoids are a neoplastic proliferation of the non granular and non secretory cells at the base of the crypts of Lieberkuhn All the three types of basal cell in the rectal mucosa together with the mature goblet cell are derived from a common entodermal stem cell This common origin accounts for the varying histological appearances seen in rectal carcinoids Stout (1942) says that the atypical or non granular form of rectal carcinoid is derived from Kultschitzky cells in an early stage of differentiation and before they have acquired the ability to produce granules He states that the festoons of columnar cells characteristic of these tumours approximate the shape of columnar crypt cells Stout s undifferentiated cells are probably identical with the non granular and non secretory basal cells referred to above It is also possible that this cell is the adult form of the original entodermal stem cell and is therefore capable of differentiating into a Kultschitzky Paneth or goblet cell However it is a curious fact that no carcinoid tumours of the atypical form seen in the rectum have been reported in the small intestine or colon It is possible that some of the carcinomas of the intestine and rectum previously reported as anaplastic or carcinoma simplex are undifferentiated forms of the atypical carcinoid

No case has yet been reported of a metastasizing carcinoid of the rectum show ing clinical manifestations such as cutaneous flushing and diarrhoea, due to the secretion of excessive amounts of 5 hydroxytryptamine Urine tests for 5 HIAA were performed, both before and after removal of the primary growth on the only case of metastasizing carcinoid seen at St Mark s Hospital but the levels have been within normal limits on every occasion This case showed cytoplasmic granules in only a few of the tumour cells It is possible that the level of urinary 5 HIAA is raised only in the ileo caecal or true type of carcinoid which shows a greater density of granularity On the other hand at least 2 cases have been reported as carcinoid with clinical manifestations in which cytoplasmic granules could not be demonstrated (Snow et al 1955 Duncan et al 1955)

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# CHAPTER 7

## PEUTZ JEGHERS SYNDROME

THOMAS L DORMANDY

### INTRODUCTION

IN these days of mass spectrography and paper colorimetry Ravitch has recently remarked it is nice to find a condition which one can diagnose from across the end of the ward It is perhaps equally remarkable that this condition—*familial gastro intestinal polyposis associated with a distinctive kind of muco-* cutaneous pigmentation—has become generally recognized only during the past 6 years and that during this relatively brief period more than 100 cases have been reported Though an accurate estimate of the syndrome s frequency is still im possible the fact that observers aware of its existence *frequently* come across more than one affected family suggests that it may be at least as common as familial polyposis of the colon A roughly comparable mutation rate would represent about 15 new cases born to healthy parents each year in Great Britain and in view of the high mortality in infancy and childhood reported in the past advances in treatment and increased chances of parenthood may lead to a steady rise in its incidence

### HISTORICAL

*In 1896 Sir Jonathan Hutchinson described twin girls aged 12 years who had a* peculiar spotty pigmentation around their mouths and brown patches on their buccal mucosa That these spots are not in any active sense pathological we may safely assume wrote Sir Jonathan for they remain non aggressive and their subjects remain in good health In 1919 in a follow up study of the twins Parkes Weber recorded that one of the twins had died 11 years later after an operation for intussusception *The* familial link between Hutchinson s pigmentation and gastro intestinal polyposis was not recognized however for another 2 years when Peutz of The Hague described the propositus of a fabulous Dutch family (Peutz, 1921 Jeghers et al 1949) This patient s genealogical table as later constructed by Jeghers covers 3 generations with 7 proved cases of the syndrome 1 probable case and 1 with the characteristic pigmentation but no evidence of polyposis Several members of the family had died from intestinal disease and 2 had suffered from nasal polyps and 1 from bladder polyps also Peutz s paper aroused little interest until 1949 when Jeghers and his colleagues carefully reviewed the literature gave a masterly account of 10 further cases and diagnosed several more in retrospect The syndrome is therefore frequently referred to in the United States of America and in some Continental countries—though not in monosyllabic France—as Jeghers or Peutz Jeghers syndrome Since then a remarkable succession of case reports from all parts of the world has shown that no country age sex or race is immune Tanner (1951) was the first to diagnose the syndrome in Great Britain—though Foster (1944) had previously reported 2 familial cases from Wales without fully appreciating the significance of the pigmentation—and during the past 3 years we ourselves have had the opportunity of investigating 21 affected members in families of English Scottish Hungarian French and Nigerian extraction (Dormandy 1957)

A compl t b bl ography f the d ome g th paper

## GASTRO INTESTINAL POLYPOSIS

With the increasing recognition of Peutz Jeghers syndrome and of gastro intestinal polyposis the individual status of the various regional polyposes of the gut may need reviewing (Following custom rather than classical derivation the word polyp is used as synonymous with benign adenoma )

In our series there were 6 patients who had had rectal polyps removed in infancy many years before the onset of small intestinal colonic or gastric symptoms or before the diagnosis of gastro intestinal polyposis was suspected Another 2 had been regarded for more than 20 years as cases of familial polyposis of the colon – and had been included as such in published series—until their small intestinal polyps and pigmentation were discovered shortly before death

That polyposis can spread from the colon to the small intestine or even skip to the distant duodenum or stomach had been noted from time to time in the past (Bensaude 1935 Halstead et al 1950 Olson et al 1951 Allen and Seamans 1955 Pollack and Swinton 1955) but whereas the colon readily reveals its polyps to the endoscopist and the radiologist polyps in the stomach may not appear until middle life and small intestinal polyposis unless suspected from the accompanying pigmentation is still poorly recognized

One of our patients was labelled a neurotic and sent to a mental home on account of her bizarre and intractable abdominal symptoms another was treated for several years as a case of idiopathic iron-deficiency anaemia Even without appreciating the significance of pigmentation or recognizing the clinical picture the past history of recurrent rectal polyps in childhood should have raised the suspicion of small intestinal polyposis in both The reverse error though less common may have graver consequences In the course of a partial gastrectomy for duodenal ulcer 1 patient was found to have multiple jejunal polyps and 2 small adenomas in his stomach He made an uneventful post operative recovery was reported as a case of small intestinal polyposis and not investigated any further Three years later he was readmitted to hospital with inoperable abdominal cancer Necropsy revealed extensive polyposis and multiple carcinomas in the distal colon

The possibility that even a seemingly solitary polyp (discovered in any part of the gastro-intestinal tract) may be but a stray or advance member of a far more widespread disorder must always be borne in mind (Figs 40 and 41)

## SMALL INTESTINAL POLYPOSIS

Difficult to visualize radiologically and supposedly obscure or erratic in its manifestations polyposis of the small intestine—unlike polyposis of the stomach colon and rectum—has for long been regarded as a surgical curiosity rather than as a clear cut clinical entity The small intestine is always affected in Peutz Jeghers syndrome whether by a solitary polyp multiple polyps or diffuse polyposis and since in such cases the diagnosis requires no more elaborate a manoeuvre than looking into a patient s mouth its natural history and characteristic clinical features are now beginning to be recognized

**Progress by segmental spurts**

Small intestinal polyposis usually advances by spurts of segmental growth Periods of quiescence between each spurt may last for many months or years and when new crops of polyps erupt they are separated from previously involved segments by varying lengths of apparently normal gut Extensive clearing operations —such as have been carried out to forestall complications or for fear of malignant change—are therefore doomed to failure One of our patients had all her small intestinal polyps removed in the course of two prophylactic laparotomies After protracted convalescence and a 4 year span of freedom from symptoms first her anaemia then her attacks of pain and borborygmi recurred At operation (her sixth) 2 intussuscepted jejunal segments were found both sprouting polyps of all shapes and sizes

**"Micropolyposis" and malignant change**

Serial sections and histological examination of operation and necropsy specimens of small intestine from patients with Peutz Jeghers syndrome may reveal areas of microscopic polyposis Around most of the major polyps and even in segments not adjacent to naked-eye growths we found circumscribed islets of micro adenomatosis in several of our cases The micro adenomas neither project into the lumen of the gut nor do they cause puckering on the peritoneal surface but embedded in the bowel wall they disrupt the continuity of its muscle coat Some are simple adenomatous vesicles which appear as if they might have grown down from the lining of the gut (Fig 36) others are more complex adenomatous nodules which spread from submucosa to subserosa (Figs 37 38) Many show considerable irregularity or perhaps immaturity of their acinar cells It is probably this irregularity together with the apparent invasion of the deeper layers which accounts for the frequent reports of malignant change and for the common statement that such a change is almost or just as liable to occur in the small gut as in the colon (Jeghers et al 1949 Aird 1952 Maingot 1955) In fact the jejunum and ileum are rarely if ever the seat of true carcinomatous degeneration

Spread to lymph nodes or liver from such secondary carcinomas has never been seen and following up reported cases in which malignant change had been diagnosed on the histology of polyps removed at operation we found that the subsequent progress of the patients invariably cast doubt on the original diagnosis In our own series there were 4 in whom malignancy had been diagnosed several years before they came under our care or observation Two remain in excellent health One had had carcinoma of the ileum diagnosed on two occasions 13 and 15 years before he died of carcinoma of the pancreas The fourth who had been forecast to have only a few months to live in 1917 died in 1956 after a heart attack

Whether or not micro adenomas are congenital (as well as genetically determined) defects of the small intestine it is highly improbable that the irregularity of their cells or their intramural position indicates even a border line state between innocence and malignancy On the contrary they probably represent an early perhaps the earliest stage in the development of naked eye polyps When such polyps give rise to complications and are surgically removed their origin from the deeper layers imparts to the histological sections a deceptive appearance of malignant invasion

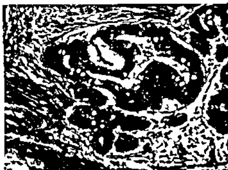


Fig 36 —Adenomatous vesicle embedded in the muscle coat of the gut from a segment of micropolyposis (haematoxylin and eosin × 360 reduced by five twelfths in reproduction) (*By courtesy of the Editor* New England Journal of Medicine )





Figs 37 38 —Adenomatous nodule from an area of micropolyposis It showed several malignant features—invasion of the deeper layers irregularity of the acinar arrangement hyperchromatic staining Had these been found in one of the more exuberant naked-eye polyps they would certainly have led to the diagnosis of carcinomatous degeneration These microscopic adenomas most of which are invisible to the naked eye probably represent the earliest stage in the development of small intestinal polyps (haematoxylin and eosin × 6 × 90 reduced by one-eighth in reproduction) (*By courtesy of the Editor of* Gastroenterologia )

**Clinical picture**

Small intestinal polyposis is not—as is often said—a diagnosis by exclusion neither should the diagnosis depend on the discovery of pigmented spots

It is true that many small intestinal polyps remain silent throughout life but when they do give rise to trouble their clinical picture is as characteristic as that of appendicitis or of duodenal ulceration The common underlying pathology is a succession of transient enteric intussusceptions These have little in common with the classical idiopathic intussusception of infants or with the secondary colonic intussusception of the elderly Whether they are caused by polyps telescoping one segment of gut into the subjacent one (Raiford 1932) by spasmodic incoordinated contractions of the bowel around the polyps (Wardill 1925) or in seemingly normal segments (probably areas of micropolyposis) by abnormal peristaltic waves (Dubourg et al 1952) the overwhelming majority undergo spontaneous reduction Though they always recur—harassing some patients for years—and though dramatic in their symptomatology they rarely lead to complete obstruction and only exceptionally to strangulation or gangrene

*Colic or wind pain*

The patient s chief complaint is attacks of green apple type of colic or wind pain Brief but frequent waves pursue an unpredictable and agonizing tortuous course striking anywhere in the abdomen often with clock like regularity 10–15 minutes after getting out of bed or after meals They rarely wake the patient at night During the attacks which do not usually last for more than a few minutes the patients can often feel a gurgling lump or several lumps moving about sinuously in their abdomens like a ball rolling to and fro as one of them described it The end is frequently heralded by the passage of abundant flatus

*Borborygmi*

Borborygmi may be a prominent and distressing feature and an undeservedly neglected symptom even between attacks of pain Jeghers mentions that in one of his cases they were audible across the ward

In one of our patients a young man aged 16 years the sudden onset of frequent explosive rumblings from the pit of his stomach were the presenting complaint In the absence of pain bowel symptoms and radiological evidence of polyposis we took no notice of this (despite the positive family history) only to be confronted with him now an acute abdominal emergency 9 months later His elder brother found the ridicule to which they exposed him more difficult to endure than his intractable con stipation or his attacks of pain And far from pointing to the correct diagnosis the mysterious noises which emanated from another patient a woman aged 30 years *finally convinced her doctors that she was a neurotic*

Diet alkalis and routine analgesics have no effect on the symptoms but self induced vomiting bending down doubling up rolling about on the floor other bodily contortions or even simple abdominal pressure may quite regularly cut short the attacks It is not surprising perhaps that hysteria figures prominently in a wide range of recorded misdiagnoses Barrington Ward (1925) commented on a case of small intestinal polyposis that though I have not seen a case before in which it was possible to reduce an intussusception in its early stages by simple manipulation through the abdominal wall this was done on at least three occa sions by two different observers Dr G Barna who looked after one of our patients a girl aged 8 years during one of her acute episodes described that as he was palpating a tender mass in her right iliac fossa she began to cry and her mother hurried into the room

Despite my entreaties she vigorously started to massage her daughter s abdomen insisting that in the past this had always eased the pains By the time I had succeeded in extricating them the previously well defined indeed visible mass had disappeared He made no secret of his belief that the mother had ruptured an *intra abdominal* abscess but despite my gloomy prognostications a few minutes later the patient passed flatus her pain and vomiting subsided and her general condition began to improve visibly

Unfortunately symptoms and signs have usually disappeared *by the time the* patient is seen by his doctor or when the family doctor actually witnesses an attack the mobile noisome lumps which he vividly describes in his note to the hospital have vanished by the time the patient arrives in the casualty department Lanman *(1939) recalls that members of the house staff* pointed out somewhat

caustically that within 24 hours she (a child who had died from gangrenous intussusception) had been seen at another hospital and had been discharged with the statement that nothing was wrong Their triumph was very short lived In going over the old history it was found that she had been seen at the Children s Hospital had been thoroughly examined and nothing was found We even sent her to the Psychiatric Service as a problem child Though gangrenous intus suceptions are fortunately rare the rest of the case history is depressingly typical (Dormandy and Edwards 1956) There is no other abdominal condition which presents with such ephemeral symptoms and signs but *plus ça change plus c est la meme chose* this in itself must be the clue to the diagnosis

*Investigations*

*Radiography*

Clinical recognition of small intestinal polyposis is the more important because radiology is so rarely helpful Several more or less elaborate techniques have been described to aid visualization (Golden 1945 Hodes and Edeiken 1949 Manteau 1952 Dedick and Collins 1953 Shell 1956) but it is fair to say that positive results always require a high degree of suspicion on the clinician s part and un common patience and persistence from the radiologist The small diluted barium meal (not more than 4 ounces) with frequent films and screening is then as likely to produce evidence of polyps as small bowel enemas or the intravenous admini stration of drugs (Fig 39) Delay in the passage of barium smears left behind irregular patterns of retained barium or shadows cast by the pedicles may all arrest the expert s attention

*Endoscopy and sigmoidoscopy*

Endoscopy can be performed only at operation but it is then a valuable pro cedure It is notoriously easy to miss small soft polyps in the small intestine especially in the jejunum A child s sigmoidoscope on the other hand can easily be introduced through a small enterotomy near the duodeno jejunal flexure and the whole small gut can be run concertina wise on to its sheath Circumscribed areas of early polyposis may thus be detected

*Haemoglobin estimations*

Haemoglobin estimations will often reveal quite a severe degree of hypochromic anaemia even in the absence of observed bleeding From benign adenomas such occult blood loss is far more common than acute massive haemorrhage (River et al 1956)

## PIGMENTATION

The pigmentation has a striking but inconstant cutaneous and an elusive but characteristic mucosal component The skin pigmentation consists of tiny clearly demarcated dark brown or black macules which are grouped around the orifices of the face—the mouth the nostrils and the eyes (Fig 42) They are neither elevated hairy tender nor vascular and their number varies from 1 or 2 to several hundred Kettron described vertical bands a characteristic microscopic distribution of the melanin particles (Jeghers et al 1949) but though we have performed biopsies on several mucosal and cutaneous spots like Troxell (1954) we have been unable to detect their presence in our own cases The palms



FIG 39 —This patient unlike most had only mild symptoms from polyps which gave rise to dramatic radio logical appearances Segments of small gut could be seen intussuscept ing and undergoing spontaneous re duction on the x ray screen and an almost Van Goghian effect was achieved by segmental spasms of the bowel around the growths



FIG 40 —Multiple polyps in the stomach made obvious by gentle pres sure on the fundus Pressure on the distal half and pictures taken after the bulk of the barium had passed on showed that the whole stomach was involved The patient aged 25 years had no gastric symptoms though frequent attacks of colic suggesting small intestinal polyposis occurred these failed to show radiologically laparotomy revealed a segment of ileum studded with polyps

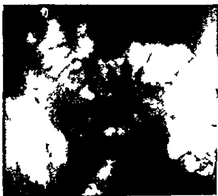


FIG 41 —Symptomless polyps in the colon of a man aged 21 years who had recurrent episodes of small intestinal intussusceptions Several members of his family—known cases of small intestinal polyposis—had died from malignant change in unsuspected polyps of the colon or rectum

and fingers are a not infrequent site for spots (Fig 44) and the toes and soles occasionally carry a few There is no general increase in skin pigmentation and none of the addisonian darkening of scars creases and the normally pigmented parts of the body Connor (1895) presenting the Hutchinson twins to the Aesculapian Society of London commented on their dark complexion and Jeghers et al (1949) Tanner (1951) and others have noted that all previously reported cases had been dark haired and of a dark complexion It is now apparent



Fig 42—Pigmented spots on the lips face and nasal vestibules No significance was attributed to these for many years despite chronic digestive symptoms They were later attributed to Addison s disease and advanced hepatic cirrhosis



Fig 43—Buccal pigmentation the *sine qua non* of Peutz Jeghers syndrome (*By courtesy of the Editor of* Gastroenterologia )



Fig 44—Pigmented spots on the palms and fingers There was also early clubbing which seems to be a frequent though inconstant association (*By courtesy of the Editor of* Gastroenterologia )



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Fig 41 —Symptomless polyps in the colon of a man aged 21 years who had recurrent episodes of small intestinal intussusceptions Several members of his family—known cases of small intestinal polyposis—had died from malignant change in unsuspected polyps of the colon or rectum

polyps were present in a member of another family described by Hafter (1954) and in 1 of our own patients (who also had a crop of bronchial adenomas) such widespread polyposis is probably uncommon

**Skeletal and cutaneous defects**

Clubbing on the other hand seems to be a real though inconstant association (Ravitch 1948 Jeghers et al 1949 Dormandy 1957) and well marked scoliosis was noted by Tanner and in 4 of our patients Familial soft tissue and bony tumours multiple sebaceous cystadenomas and dyschondroplasia have been described both with familial polyposis of the colon (Bensuade 1935 Gardner and Richards 1953 Oldfield 1954 Weiner and Cooper 1955 Zanca 1956) and with gastro intestinal polyposis (Devic and Bussy 1912 Cabot 1935) and 1 of our patients with Peutz Jeghers syndrome had bilateral tibial exostoses It is unlikely that the fortuitous mutation of the two dominant genes is responsible for such combinations and gene modifiers would have a constant effect within 1 family The syndromes are almost certainly true breeding variations such as occur in several other rare conditions (for example pachyonychia congenita) Such diseases tend to crop up in new families with additional abnormal features constantly being added to existing ones

**Visceral disease**

Congenital heart disease which was found at necropsy in one of Jeghers and one of our own cases may reflect a general lowering of the threshold of phenotypic expres sion which is not unusual in genetic disorders Two of our patients also had large peri vaterian duodenal diverticula 1 had extensive jejunal and ileal diverticulosis and 3 had colonic diverticulosis or diverticulitis

**Retarded development**

Retarded development and lateness of maturity have been reported or implied in a number of cases (Niemack 190_ Mandillon and Georget 1935 Je_hers et al 1949 Hillemand et al 1952 Kaplan and Feuchtwanger 1953) but severe iron deficiency anaemia so frequently complicates polyposis that even without a history of frank bleeding it is hard to exclude occult blood loss as an intermediate cause

**Ovarian abnormality**

In a surprisingly high proportion of cases some ovarian abnormality has been found either at operation or at necropsy The lesions have been mostly multiple simple cysts but large solitary cystadenomas and a variety of malignant tumours have occa sionally been found (Devic and Bussy 1912 Dickson 1944 Jeghers et al 1949 Tseng and Braunstein 1954 Berkowitz et al 1955 Dormandy 1957)

## MANAGEMENT

Unlike polyposis of the colon—which must always be excluded or treated on its own merit—small intestinal polyposis is neither amenable to prophylactic surgery nor requires it

**The symptomless patient**

At the risk of cancerophobia (by no means remote on account of the frequently positive family history) patients with pigmentation must be told that even though they have no symptoms they are potential carriers of small intestinal polyps Many unnecessary operations and misplaced incisions could have been avoided if in strange casualty departments as acute abdominal emergencies they could have given this information to the surgical registrar on call Children with pig

that the syndrome quite frequently affects fair haired and light skinned people but it would seem that the spots especially the cutaneous ones are less prominent in such cases

The cutaneous pigmentation usually appears at birth or in infancy and often begins to fade at about the time of puberty Not uncommonly by the age when small intestinal polyps tend to be at their most turbulent—the second and third decades—the spots on the face have disappeared completely or have become so sparse and pale that they are easily buried under a coat of face powder and lip stick By contrast the mucosal pigmentation persists throughout life and Jeghers therefore regards it as the *sine qua non* of the syndrome The buccal mucosa is always affected (though not the tongue) occasionally the palate the fauces the nasal vestibules and the conjunctivas (Fig 43) The mucosal pigmentation is more blotchy and lighter in shade than the cutaneous macules and it is all too frequently missed (Whereas looking at the patient s face and protruded tongue is one of the most primitive surgical reflexes careful search of the inside of the mouth especially when faced with an acute abdominal emergency is often omitted ) Neither the intestinal mucosa nor the polyps themselves are pigmented

## HEREDITY

The syndrome is inherited through a mendelian dominant gene of high penetrance a pattern of inheritance similar to that of familial polyposis of the colon Because of the earlier onset of complications and diminished chances of parenthood how ever the fitness value of Peutz Jeghers syndrome had probably been far lower in the past and it is reasonable to assume a correspondingly higher mutation rate Whether a single gene is responsible for the two different manifestations pigmentation and polyposis or two closely linked genes mutate synchronously there are certainly no grounds for believing that the pigmentation is in any way secondary to gastro intestinal dysfunction (Bradford and Danzig 1950) Pigmenta tion of the skin and mucous membranes is an occasional feature of many digestive disorders and deficiency states—coeliac disease the sprue syndrome ankylosto miasis schistosomiasis gastro-colic fistulas carcinomatosis Whipple s disease and pernicious anaemia—and has indeed been described with other ectodermal defects as a secondary manifestation of gastro intestinal polyposis (Cronkhite and Canada 1956) but both the character and the distribution of such secondary pigmentation are quite unlike the scattered macules of this syndrome

The extent of the pigmentation in the Peutz Jeghers syndrome bears no relation ship to the severity of the gastro intestinal symptoms indeed several members of affected families may have striking pigmentation and still remain free from intes tinal symptoms throughout life

The hutchinsonian spots are occasionally seen without polyposis or a positive family history perhaps as a result of sporadic mutation and incomplete penetrance of the peccant gene or in patients who harbour microscopic but no naked eye polyps

## ASSOCIATED ABNORMALITIES

**Widespread polyposis**

Peutz referred to his syndrome as visceral polyposis because 3 members of his patient s family had bladder and nasal as well as gastro intestinal polyps Though bladder

servative It is better to remove a polyp than to resect a segment and it is better to resect several segments than to try to save time rather than gut by removing varying lengths of normal intestine between two diseased areas

Polyposis in the small bowel should always be regarded as a potentially progressive disorder which may eventually involve its whole length and however much patient and surgeon may deplore repeated nibbling operations they are preferable to a state where no small gut is left to be nibbled away

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mentation should also have periodic haemoglobin estimations though it is un justifiable to subject them to repeated barium studies

Genetic advice depends so much on the individual s sense of values that it is not a question on which one can dogmatize Since the syndrome does not skip genera tions members of affected families who have no pigmentation can be told that *they and their children* are *highly unlikely* to suffer from polyposis The descen dants of those with pigmentation have a 50 per cent chance of being afflicted but it is reasonable to say that the disorder is a small hazard to life so long as they live within the reach of good surgical care From the eugenic point of view the syndrome can never be out bred because of the constant if not increasing mutation rate and it is therefore quite unjustifiable to recommend childlessness An affected person with unusual abilities can be expected to have offspring of greater value to the community than the average person with immaculate lips and at present the minority of patients who ask for genetic advice are those whose intelligence and sense of social responsibility is a trait that far outweighs a few polyps

### *The chronic case*

The patient with infrequent or mild attacks must realize that a permanent cure cannot be assured even if all polyps present at any one time are removed On the other hand operation may bring relief for many years and possibly for life and carries only a slight risk Chronic blood loss should certainly not be allowed to suck out a child s vitality even if unattended by pain nor should adult patients be allowed to drift into a state of morbid preoccupation with their bowels or be labelled neurotics if loud borborygmi turn them into social misfits For mild symptoms however they themselves are more likely to discover some homely measure of relief than their doctors

### The acute episode

Acute attacks are rarely acute in the sense that they require an emergency operation Small intestinal intussusception need not conjure up the image of impending strangulation and gangrene (though of course these complications must be watched for) Antispasmodics and especially repeated enemas will often terminate the attack and allow the operation to be performed as an elective procedure

Not only are patience and judgment apt to be lacking when surgery is under *taken as a life saving measure* but *polyps in the stomach and colon* which should influence both pre operative preparation and the scope of the operation often elude the most sensitive fingers at laparotomy With the drip and suck con servative régime however it is important to remember that intestinal tubes will not only thread their way through incomplete enteric intussusceptions (Amesur 1953) but it is possible that they may even stimulate irregular peristalsis and encourage other segments to intussuscept

### Elective procedures

Though hard and fast rules cannot be laid down for a disease so diverse in its manifestations the surgeon s attitude to small intestinal polyposis must be con





Fig 45 —Male aged 81 years 5 years abdominal pain immediately after meals Barium meal 5 4 56 Volvulus of stomach on its long axis duodenal and jejunal diverticulae present



Fig 46 —Male aged 63 years mild dyspepsia for 25 years severe pain for 6 months Barium meal 25 6 51 Moderate sized gastric ulcer just below angulus with shortening of lesser curvature diverticulum in the upper part of the body of the stomach



Fig 47 —Female aged 80 years dyspepsia for 30 years 9 haematemeses 4 in one year Barium meal 17 4 47 Gross shortening of lesser curvature Gastric ulcer with pyloric canal opening from it Large gastric sump hour glass contraction of the B type

# CHAPTER 8

# RADIOLOGY OF THE STOMACH DUODENUM PANCREAS AND SMALL INTESTINE

F PYGOTT

*A radiograph is a record of the picture at one given moment only whereas the diagnosis is made and can only be made by a series of patient observations made at intervals*

A E BARCLAY

## INTRODUCTION

THE purpose of this chapter is to discuss briefly the radiological aspect of some of the *important conditions encountered in the stomach small bowel and pancreas* which in the author s opinion give considerable diagnostic difficulty

Radiological abnormalities of form or function in the alimentary tract are often capable of alternative explanation in terms of pathology and it may not be possible to be certain of the nature of a clearly demonstrated gross lesion on radiological grounds alone It is therefore of the utmost importance that an accurate clinical history and all ancillary information should be available fully to the radiologist and that these should be given his consideration when an examination is performed and subsequently at the time of reporting Nevertheless it is a mistake for the radiologist to be biased strongly by the clinical information and so to twist the interpretation of *his* findings to conform to a preconceived diagnostic possibility It is equally a mistake for the clinician to deny any relevance to definite radiological evidence of an abnormality because its probable cause would not appear to fit in with his *own concept of the nature of the condition present* Symptoms in gastro enterological cases may be far from clearly defined and the difficulties in diagnosis increase the responsibility of the clinician and the radiologist it is essential that they confer freely and that they respect each other s opinion while mutually recognizing their fallibility

## GROSS DEFORMITIES OF THE STOMACH

Deformities of the stomach (Figs 45–47) may be described as rotational intrinsic or extrinsic or a combination of these When the deformity is gross radiological *examination can be extremely difficult*

### Rotational deformity

Rotational deformity due to twisting on the long axis of the stomach results in varying degrees of cascade stomach from the simple symptomless cup and spill type to the extreme so called volvulus of the stomach associated with symptoms of *aero gastrique bloque* (Roussel 1952) Rotation on the short axis of the stomach is most often encountered in large para oesophageal hernias *of the rolling type and* adds greatly to the task of demonstrating an unassociated lesion especially when this is situated near the area of maximum distortion However one of the features of *rotational deformity* is its inconstancy and an ulcer or other lesion may be shown

neoplasia in gastric ulceration has varied in the opinion of different observers MacCarty (1940) in his Carman lecture stated that 90 per cent of all chronic gastric ulcers over 2 5 centimetres in diameter are neoplastic though in actual figures he produced only 14 5 per cent of these large ulcers were shown to be so histologically His opinion has been widely quoted A number of reported series now indicate that this opinion was incorrect Ledoux Lebard et al (1945) reported that 24 of 28 ulcers over 3 centimetres in diameter were benign Russell et al (1948) that 26 of 35 ulcers over 2 5 centimetres were benign on section and 5 had a medical follow up of more than 5 years Stevenson and Yatse (1949) that 18 of 20 ulcers over 2 centimetres in diameter were simple Lumsden (1951) reported that 11 out of 15 ulcers 3 centimetres in diameter or over were benign and Jennings and Richardson (1954) in an excellent paper discuss the diagnostic problems and report a similar experience

Kirsh (1955) reviewed a series of 120 simple and 22 malignant ulcers of the stomach discovered at routine examination and observed that 72 per cent of ulcers over 2 5 centimetres were simple but that 41 per cent of the neoplastic ulcers were of this size Lloyd and Morris (1956) had only 3 cases of giant ulcer in their series of 23 patients with neoplastic ulcer Bille and Romcke (1949) however had 15 examples of neoplastic ulcer 2 5 centimetres or over in diameter in 26 cases where the ulcer had originally been thought to be benign in a series of 908 gastric ulcer patients treated in the medical department

Personal experience and fair comment on the published series lead one to the opinion that the possibility of a large ulcer being simple or neoplastic rests not on its size but on features independent of it These distinguishing features may some times be more difficult to demonstrate or to interpret owing to the size of the lesion The difficulty of distinction is not confined to the radiologist and at operation some of these ulcers may be regarded as inoperable cancers on account of their appearance and the presence of glandular enlargement and mesenteric infiltration may confirm this diagnostic error Ledoux Lebard et al (1945) have referred to these ulcers happily as the pseudo tumerale group

**Duodenal**

Most ulcers in the duodenum are less than 1 centimetre in diameter but cases of giant ulcer occur and may cause gross error in diagnosis unless the possibility is kept in mind These giant ulcers may be so large as to replace the duodenal cap entirely and the crater may be mistaken for it (Fig 48)

The relatively few instances of giant duodenal ulcer reported nearly all indicate diagnostic errors due to lack of appreciation of the radiological appearance Brdiczka (1931) reported 3 cases Knutsson (1932) reported 3 simple giant ulcers and 1 neoplastic ulcer in the duodenum none of these was diagnosed radiologically

Freedman and Goehring (1940) considering diagnostic errors in ulcerative lesions of the stomach and duodenum reported 2 cases They remark that the ulcer is easily mistaken for a normal or slightly abnormal bulb and in 1 of their cases this error was made they further state that there is no mucosal pattern and the whole ulcer fills suddenly and is unchangeable in form The pars superior of the duodenum may be constricted distal to the ulcer which is more spherical than the normal cap and retains barium persistently Elkin (1941) reported a single case in which repeated barium examinations had been negative and the patient was even

much more easily at a second examination than at the primary examination a few days earlier

**Intrinsic deformity**

Deformities of the stomach from intrinsic causes present radiologically as contractions of the whole or part of the stomach or as irregularities of its lumen Uniform contraction of the whole or part of the stomach is almost synonymous with neoplasm though occasionally dense peri gastric adhesions of an inflam matory nature may simulate a local infiltrative lesion Axial contraction most marked on the lesser curvature is due as a rule to old standing gastric ulceration in the angulus area of the middle third of the lesser curve Cases reported by Hinds and Kemp Harper (1952) illustrate how in this type of deformity the pylorus is drawn up towards or even into the gastric ulcer crater and that a deep incisura may be produced in the greater curvature of the pyloric antrum Severe contrac tion of the lesser curve results in the dependent part of the body of the stomach forming a sump which cannot empty its contents A similar appearance of gross shortening of the lesser curvature may occur with neoplastic ulceration in this *region*

Intrinsic contraction transverse to the axis of the stomach produces the hour glass type of deformity When simple in nature this is of the B type (Buckstein 1953) The contraction is almost entirely from the greater curve towards the lesser and the space between the upper and lower sacs is at its narrowest not more than twice the thickness of the normal stomach wall In the neoplastic hour glass the contraction may be deceptively smooth but both curvatures are displaced towards each other and the narrowest part of the intervening space between the sacs is greater than twice the thickness of the normal stomach wall

Irregularities of the gastric lumen may be due to local neoplastic involvement to projection of hypertrophied gastric folds or to the presence of simple tumours of the stomach wall Grossly hypertrophied gastric folds may simulate an encephaloid carcinoma or lymphoma A smoothly outlined polypoidal encephaloid carcinoma in the fundus may resemble a leiomyoma but the carcinoma usually shelves in more gradually into the adjacent part of the stomach and the transition is not as abrupt as in the simple tumour

**Extrinsic deformity**

Deformities of the stomach due to extrinsic pressure may be due to enlargement of any abdominal organ and the study of the direction of displacement may give valuable help in the search for the primary lesion

## GIANT PEPTIC ULCERS

**Gastric**

An elderly person is often referred for barium meal examination with a history of a few months or weeks epigastric discomfort or pain anorexia loss of weight and secondary anaemia and the provisional clinical diagnosis of carcinoma of the stomach The examination may show a large gastric ulcer with a crater over 1 inch in diameter

The significance to be attached to the size of the crater as an indication of

important to recognize that a large ulcer is present than it is to be certain of its site since many of these patients die of haemorrhage unless a positive diagnosis is made Surgical exploration may not provide conclusive evidence of the nature of the ulcer and this may be shown only histologically

## RADIOLOGICAL DIAGNOSIS OF DUODENAL ULCER

The radiological demonstration of evidence of a duodenal ulcer may be a matter of real difficulty and repeated barium meal examinations may have failed to reveal it (Fig 49) though the patient s later history may fully confirm its existence

### Plethoric patients

Most trouble is encountered in plethoric persons in whom the duodenal cap is often situated behind the pyloric antrum and directed backwards With the patient in the erect position the first part of the duodenum may never be completely outlined though the stomach is emptying rapidly It is essential in such cases to make free use of the supine and prone rotated projections Gas relief filling of the duodenal cap by the method of Hampton (1937) is valuable and this has been confirmed by many including Meyer (1952) and Hinkel and Moller

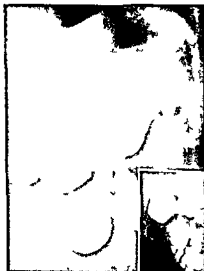


FIG 49—Male aged 52 years 7 years dyspepsia with pain not related to meals Pain going into back unrelieved by food Three barium meals negative and gall bladder removed at laparotomy 3 years ago No relief of symptoms Barium meal 23 11 53 Duodenal cap not deformed but ulcer shown through the empty pyloric antrum in the posterior wall of the post bulbar region Laparotomy 1 12 53 confirmed site of ulcer which was penetrating pancreas



FIG 50—Male aged 63 years 10 years dyspepsia with pain after meals and recent melaena Barium meal 10 3 55 Large post bulbar ulcer on the medial wall of the upper part of the descending duodenum with some associated constriction of the lumen Examination repeated on 18 4 55 Ulcer much smaller No operation

regarded as insane by his wife and neurotic by his physicians Autopsy following severe haematemesis and melaena revealed a duodenal ulcer 5 × 3 centimetres in size Evashwick (1951) reported a similar error demonstrated by autopsy following a severe haematemesis—the ulcer was 6 × 5 centimetres in size

Bullock and Snyder (1952) reported the case of a man aged 66 years diagnosed radiologically At operation a stony hard mass involved the distal stomach and upper duodenum the pylorus could not be recognized and the transverse colon was adherent to the mass A block dissection with partial gastrectomy partial pancreatectomy and colonic resection was performed on the assumption that the



FIG 48 —Male aged 58 years 10 years dyspepsia with pain Recent vomiting with weight loss Barium meal 8 3 56 Very large duodenal ulcer replacing the cap Laparotomy 28 3 56 Large duodenal ulcer adherent to pancreas and liver

condition was neoplastic The appearance of the mucosa round the ulcer in the excised specimen suggested that it was gastric and not duodenal Histology confirmed the radiological opinion that the ulcer was in fact duodenal

The margin of the crater in these large ulcers may be so firm and broad that it produces a broad corona round the ulcer which cuts it off from the descending part of the duodenum and makes a smooth indentation in the pyloric end of the stomach most marked in the lesser curve side A persistent gas bubble may be present in the empty duodenal cap area as noted by Evashwick (1951)

The presence of a recognizably normal duodenal cap beyond a large pyloric gastric ulcer is a most valuable feature in distinguishing it from a giant duodenal ulcer unfortunately it is not always easy to demonstrate this satisfactorily It is inevitable that mistakes of radiological location will occur but it is far more

inspected and palpated and frozen sections made If the lesion is still questionable the antrum should be resected

Radiologically these atypical deformities of the antrum may be irregular or conical in shape (Fig 51) the degree of the deformity may be entirely constant during the examination or it may vary though maintaining a constancy of character There may be local irregularities in outline as well as a more uniform constriction The antrum or a part of it may remain so contracted during the barium meal examination that it is impossible to observe any peristalsis in the area or to demonstrate effectively any mucosal pattern In spite of gross antral contraction



Fig 51 —Female aged 74 years 2 years vomiting fluid 1 year of anorexia and epigastric pain Barium meal 31 3 54 Serial of antral region top row before intravenous morphine 0 1 grain bottom row after morphine Constant constriction in the proximal antrum with shallow recessed ulcer on the lesser curve at the constriction Distal antrum irritable and difficult to fill before morphine was given but was shown to be normal afterwards Diagnosis—antral ulcer of uncertain nature Later examinations showed no real change but final decision probably neoplastic Laparotomy 20 10 54 Prepyloric ulcer apparently benign Small glands present Partial gastrectomy Section of glands showed no evidence of growth Section of the ulcer Benign gastric ulcer but carcinoma *in situ* at one edge of the ulcer Progress 9 4 56 losing weight and poor appetite

there may be no evidence of pyloric obstruction Ingersoll (1952) has rightly stressed the importance of using all available techniques including Hampton s manoeuvre in the examination of the antrum Intravenous morphine 0 1 grain as suggested by Stossel (1953) may be valuable in relaxing areas of spasm and by increasing the depth of the peristaltic contractions may show areas of organic irregularity constriction or non-contraction in relief Pyloric relaxation also occurs and the rate of gastric emptying is increased an effect which is sometimes useful in studying duodenal lesions The rapidity of the morphine effect makes its practical value all the greater since it can be used directly after all available information has been obtained by routine methods and the entire examination can be completed in one session At times further information can be obtained by

(1956) It is also useful to record the appearances of the duodenal cap area through or just above the almost empty pyloric antrum with the patient in the supine position and rotated to the right

**Post bulbar duodenal ulcers**

Many small series of cases of post bulbar duodenal ulcer (Fig 50) have been reported thus Robinson (1934) reported 4 cases Sussman (1935) 8 cases Borman (1943) 7 cases Ball et al (1948) 6 cases Samuel (1952) 12 cases and Preiskel (1952) 2 cases but the condition is not rare The ulcer is usually situated on the concavity of the duodenal loop immediately beyond the cap and on the posterior wall but it may be on the convexity of the loop or on the anterior wall There may be a deep notch in the duodenal wall opposite to the ulcer crater and even gross stenosis so severe as to obscure the presence of the ulcer The stenosis may result in over filling of the duodenal cap during the barium meal and the normal cap and the filled pyloric antrum may obscure both the ulcer and the stenosis in several projections The ulcer is often best shown in the prone right anterior oblique or supine left anterior oblique positions using a small quantity of barium suspension only In the supine position the ulcer may again be best shown through the gas distended or empty pyloric antrum The value of exaggerated oblique views in the prone and supine positions has been rightly stressed by Ball et al (1948) and by Samuel (1952)

The medical histories of patients with post bulbar ulcers are often serious with repeated bleeds vomiting and severe back pain Persistent ulcer symptoms negative laparotomies and negative barium meals form almost a diagnostic triad Graham (1938) referred to them as occult ulcers and quoted a patient who had 3 negative laparotomies—his experience is not unique Post bulbar ulcers may be deeply buried in the head of the pancreas and not easily be seen palpation such as is possible in this area is often unsuccessful unless persistent attention is directed to the exact site The value of concentrated radiological exploration of this region of the duodenum is thus considerable

## ATYPICAL DEFORMITIES OF THE PYLORIC ANTRUM

Deformity of the pyloric antrum may occur with gastric carcinoma with gastric ulcers situated at or below the angulus or in the antrum itself or it may be associated with juxta pyloric duodenal ulcer Extrinsic pressure deformities of the antrum may accompany pancreatic cysts or tumours or even growths in the transverse colon extending through the mesocolon to the stomach or pancreas adhesions following gall bladder disease may deform it (Jenkinson and Hamernik 1948) It is the atypical deformities of the pyloric antrum for which no obvious reason is evident that present real diagnostic difficulty radiologically and clinically At operation the surgeon may be faced by the necessity of making a serious decision on very uncertain grounds when a biopsy may be inadvisable Kennedy (1952) speaking from his own surgical experience has stressed the impossibility on occasion of distinguishing certain inflammatory diseases of the stomach from infiltrating types of cancer by handling and viewing the surgically removed specimen Jenkinson (1954) in his Caldwell lecture says Opening the abdomen and palpating the pyloric antrum is not enough The stomach should be opened

The plaque has an increased rigidity compared with the surrounding stomach and this may be responsible for typical appearances thus it may produce a sus picious straight line effect in part of the smooth curved line of the lesser curvature or if near the greater curvature in the dependent part of the stomach it may cause an abrupt flattening of the normal bulge When the plaque is situated on the anterior or posterior wall of the body or antral parts of the stomach an uneven density in the barium shadow may be observed in the filled areas On light com pression during screen examination it may be easy to see through the filled areas in which the plaque is situated Fundal plaques remote from the cardiac orifice can be very difficult to detect due to the very wide individual variations in the



FIG 52 —Male aged 70 years 1 year s loss of energy and 6 months of epigastric discomfort Barium meal 31 7 51 Erect film of barium filled stomach showed a slightly wavy appearance of the middle third of the lesser curvature not apparently abnormal Supine film showed a plaque of growth in this area Laparo tomy delayed until 10 10 51 Presence of growth confirmed Total agstrectomy

normal appearance of the gastric fundus In the absence of a hiatus hernia or other cause of deformity of the fundal gas pattern a small and smoothly rounded fundus should excite attention and every effort should be directed to demonstrating its distensibility and the character of its mucosal pattern When the cardiac orifice is involved at an early stage though the patient may complain of slight or in constant dysphagia quite thick barium cream may be swallowed with little or no hold up or other abnormality being detected it is well in these cases to use a solid or semi solid core of bread dipped in barium before dismissing the *complaint* as imaginary it is very rare indeed for true dysphagia to have other than an organic

employing gastric insufflation through a Ryle s tube with the stomach containing only a small quantity of moderately thick barium suspension an extension of the Hampton manoeuvre

Despite all efforts there will remain a group of cases in which the nature of the deformity remains uncertain A proportion of these will be submitted to laparotomy and in some of them the surgeon will observe some slight thickening of the pyloric end of the stomach and will regard this as being due to scarring from a small healed ulcer—a proportion of these will be shown histologically to be small carcinomas There is no doubt that in the absence of clinical indication for laparotomy these undiagnosed antral deformities require very careful radiological observation and that laparotomy may need to be pressed for in the complete absence of confirmatory findings It is a mistake to be lulled by lack of gastroscopic confirmation positive evidence from this source may be very valuable but negative evidence may be quite misleading Balint and Slater (1954) reviewing cases of obscure antral deformity have referred to the gastroscopic error of believing *that the whole antrum has been seen when in fact a large part has not* McGlone (1952) has also mentioned the unwarranted sense of security sometimes engendered by gastroscopy in some cases of antral disease The radiologist s responsibility in the diagnosis of atypical antral deformity is very great and honest doubt as to the simplicity of a lesion must be shared freely with clinical colleagues who in turn must be prepared equally to accept the possibility of error in any action they may take

## RADIOLOGICAL DIAGNOSIS OF SMALL CARCINOMAS OF THE STOMACH

Small neoplasms of the stomach are often referred to as early ones but this is not necessarily correct for the mere size of a growth is not always an indication of its recent development or of the limitation of its remote extensions (Fig 52)

### The parietal plaque

The parietal plaque a local thickening of the mucosa and submucosa is a feature of these small neoplasms and the outline of the barium filled stomach is locally set back towards the lumen of the viscus by it Mucosal relief patterns in the plaque area show either loss of normal fold pattern or local rigidity of the rugae Ulceration on the surface of the plaque may occur producing the appear ances described by Gutmann et al (1939) as the niche en plateau which may be *likened to the imprint of a coin on a plastic substance a flat shallow ulcer with a* narrow projecting margin If the plaque is thicker ulceration on its surface may appear as la niche en plateau encastre a shallow ulcer on the surface of a filling defect If ulceration progresses so that it destroys the central part of the plaque to a considerable extent the appearance of la niche d aspect banal encastre follows and an ulcer simulating a simple gastric ulcer results but fitted into a filling defect Carman (1921) in describing his classical meniscus sign stated that the absence of a classic projecting niche is one of the principal differential characteristics of malignant ulceration and that the disintegration of the central portion of the plaque formed crater *surrounded by a ridge of carcinomatous tissue block* was responsible for the meniscus appearance

**Pancreatic calculi**

Pancreatic calculi are visible in the plain film of the abdomen When they are numerous the general outline of the gland may be traced as it runs from the curve of the descending part of the duodenal loop upwards and to the left to the hilum of the spleen This upward inclination is steeper than experience in the cadaver would lead one to expect Buckstein (1953) and Kemp Harper (1949) have illus trated excellent examples of the condition

**Acute pancreatitis**

In acute pancreatitis marked swelling of the head of the pancreas may result in upward displacement of the pyloric end of the stomach and first part of the duodenum and in stasis in the duodenal loop (Case 1940) Poppel (1954) who has made extensive contributions to the radiological investigation of pancreatic disease states that in relapsing pancreatitis the duodenal loop may be widened the midline retrogastric soft tissues increased and the duodeno jejunal flexure displaced downwards He also states that areas of spasm and peristaltic irregulari ties occur in the duodenal loop with coarsening of the feathery jejunal mucosal pattern and that the definition of the properitoneal fat layer may be decreased due to oedema of the abdominal wall Ludin (1952) has illustrated a case of pan creatitis showing Frostberg s sign

**Cysts**

Pancreatic cysts produce smoothly outlined displacement and compression alterations in the outlines of adjacent viscera varying with the site of origin of the cyst and its direction of extension (Case 1940 Kemp Harper 1949 Buckstein 1953)

**Cancer**

Broadbent and Kerman (1951) reviewing the films of 76 out of 100 known cases of pancreatic cancer found that sufficiently clear cut evidence was present in about 50 per cent to suggest the correct diagnosis The experience of Hodes et al (1954) in reviewing records of 105 patients was similar Sifre et al (1953) found a significant abnormality in 16 out of 34 patients examined by barium meal and Pygott (1950) found abnormalities in 16 out of 25 patients Berk (1941) noted that 14 out of 31 cases were recognized as abnormal at the time of reporting but when reviewed retrospectively this number has increased to 20 There is no doubt that increased awareness results in an increased number of positive findings

**Tumours of the head of the pancreas**

Tumours of the head of the pancreas may stretch out the duodenal loop either generally or locally or the descending part of the loop may be displaced forwards by the enlargement of the gland extending behind it (Figs 53 54 and 55) Con strictive deformities may be produced in the horizontal portion of the first part of the duodenum and these may simulate stenosis due to a post bulbar duodenal ulcer Duodenal ulcer may of course co exist and was present in 3 cases in the series reviewed by Broadbent and Kerman (1951) and in 4 of 162 cases by Beeler and Kirklin (1952) Three cases of duodenal ulcer and pancreatic cancer were

basis The presence of the plaque in any area of the stomach interferes locally with the peristaltic contractions which pass it by unaltered in shape

**Atypical contractions and localized constrictions**

Difficulties that may be encountered in the diagnosis of cases showing atypical contractions of the pyloric antrum have been referred to already

Localized constrictions may occur in the pyloric antrum or in the body of the stomach and though these may be deceptively smooth in outline they are nearly always neoplastic Simple hour glass contractions of the stomach are very rare in men and any hour glass contraction occurring in a man is almost always neoplastic

**Localization**

Ulcers in the distal antrum are to be regarded with suspicion Holmes and Hampton (1932) found that carcinoma in the pyloric end of the stomach was nearly twice as frequent as simple ulceration If an antral ulcer crater is surrounded by a broad perimeter due to a rolled edge or shows a large triangular niche (Gutmann et al 1939) it should certainly be regarded as neoplastic

The exact site of an ulcer at the pylorus may be difficult to decide as the position of the pyloric ring may not be identifiable owing to the deformity associated with the ulcer Ivie and Beveridge (1954) found that in 6 cases of acute ulceration at the pylorus or on its gastric side the ulcer was eventually shown to be duodenal Ettinger (1950) has remarked on the same difficulty in localization due to gaping of the pylorus with duodenal ulcers situated so close to the pyloric ring as to be mistaken for antral gastric ulcers At operation a competent surgeon may not be able to do more than confirm the presence of an ulcer of uncertain nature

It is well to realize that the diagnosis of small neoplasms of the stomach does not rest on the application of any one sign as a sort of golden rule but on the correct appreciation of the appearances which may be produced by the morbid anatomy present Thus it used to be taught that ulcers of the greater curvature were always malignant yet Kirsh (1956) has reported a series of 8 cases of which 6 were simple and Ochsner (1956) has reported 7 benign ulcers of the greater curvature in a series of 148 surgically resected gastric ulcers When the appearance of the morbid anatomy present is non specific as it may be no specific radiological interpretation is possible Nevertheless the demonstration of a definite lesion of uncertain nature in the stomach may be a most important positive contribution to a difficult clinical diagnosis

## RADIOLOGICAL CONTRIBUTION TO THE DIAGNOSIS OF PANCREATIC DISEASE

Pancreatic disease presents more difficulty in diagnosis than almost any other abdominal condition and the lack of any suitable excretory contrast medium is a serious handicap to the radiological investigation In spite of this handicap radiology can provide diagnostic information of value in 50 per cent or more of the cases of pancreatic tumours and in nearly all cases of pancreatic cyst or calcification It has a contribution to make in the diagnosis of acute and chronic or relapsing pancreatitis and the functional disorders of the small bowel associated with pancreatic steatorrhoea may also be studied

the normal rapid alteration in mucosal fold pattern in the duodenum which they regard as early evidence of infiltration Poppel and Marshak (1944) point out that when the common bile duct runs transversely behind the descending part of the duodenum as happens in a proportion of cases dilatation of the duct may dis place this part of the duodenum forwards and medially as it crosses the duct

**Neoplasms of the body of the pancreas**

Neoplasm of the body of the pancreas may displace the body of the stomach forward as it crosses in front of the lumbar spine A retrogastric mass in the body



Fig 54 —Female aged 46 years 5 months lassitude Recent lower abdominal pain Melaena and anorexia Mass in pouch of Douglas Liver enlarged No jaundice Barium meal 9 4 54 Annular constriction in the post bulbar area of the duodenum Diagnosis—carcinoma of pancreas Post mortem 29 5 54 No jaundice Growth in head of pancreas invading the second part of the duodenum and gall bladder



Fig 55 —Female aged 57 years 3 months epigastric pain and back ache Recent vomiting No loss of weight Barium meal 8 5 54 Constrictive lesion in the third part of the duodenum Diagnosis—carcinoma of pancreas Laparotomy 16 5 54 Carcinoma of head of pancrea displacing the duodenum forwards and involving it Metastases in liver Palliative gastro-enterostomy

or tail may produce a pressure filling defect in the stomach when the patient is tilted backwards from the standing to the supine position (Case s pad sign) The stomach may be directly infiltrated as in tumours of the head of the gland The duodeno jejunal flexure may be flattened and displaced downwards or there may be compression of the proximal side of the splenic flexure Direct extension from growths of the body may take place to the lumbar spine with resulting vertebral collapse Scott (1952) has illustrated a case of carcinoma of the body of the pan creas in which a fistula had developed from the stomach through the growth to the lumbar spine which was involved Neoplasms in the tail of the pancreas

reported by Dashiell and Palmer (1947) and Forty and Barrett (1952) have reported a case of peptic ulcer in the third part of the duodenum associated with an islet celled tumour of the pancreas

**Constrictive and infiltrative lesions**

Constrictive and infiltrative lesions of the second and third part of the duodenum are probably the most frequent abnormalities detected radiologically in carcinoma of the head and body of the pancreas 59 examples of this type of involvement were found by Broadbent and Kerman (1951) in their series The medial displacement of the lateral wall of the descending duodenum which usually occurs with an



FIG 53 —Male aged 54 years 3 months epigastric pain Anorexia and weight loss Jaundiced for a few days Barium meal 30 3 53 Over filling of duodenal cap and proximal portion of the second part of the duodenum with constrictive lesion in its distal part Diagnosis—pancreatic cancer Laparotomy 10 4 53 Large neoplasm of head of pancreas gall bladder and common bile duct distended resection impossible owing to involvement of the superior mesenteric vessels

annular pancreas (Dodd and Nafis 1956) is rare in pancreatic growths The reverse 3 sign of Frostberg (1938) is a special instance of an infiltrating lesion occurring around the major and minor duodenal papillae (Stiennon 1956)

The duodenal cap and pyloric end of the stomach may be smoothly indented from below and displaced upwards by neoplasm of the head of the pancreas Mucosal defects may occur in the stomach due to direct extension of the growth into it and the distinction from a primary gastric carcinoma may be impossible radiologically Hodes et al (1954) direct attention to the importance of recognizing the imprint of the dilated common bile duct in the pars superior of the duodenum which is best seen in the right anterior oblique prone position and to the loss of

flocculable barium sulphate suspension gives good results The patient is encouraged to adopt the prone position for the first 2 hours of the examination as this induces a more even distribution of barium through the intestinal loops and tends to prevent all of it lying together in adjacent loops especially when the lower ileum has been reached The flocculable suspension shows clearly the clumping type of pattern encountered in steatorrhoea and coeliac disease The work of Ardran et al (1950) and Golden (1950) has demonstrated that the type of small bowel pattern produced varies with the use of flocculable and non flocculable barium suspension and this difference has been a real source of confusion in the past

**Fractional interval feeding**

Where symptoms of an obstructive nature are to be investigated fractional interval feeding as suggested by Pansdorf (1937) may be more effective in demonstrating the lesion especially when skip areas may be present as in Crohn s disease In this method a 2 ounce volume of barium sulphate suspension is given at the commencement of the examination and further doses are given at regular intervals of ½–1 hour This enables all parts of the small bowel to be examined repeatedly during the same examination It is clear that the method should not be used in an acute obstruction

**Ice water technique**

When it is desired to outline the lower ileum completely and to distend it to its capacity the ice water or ice saline technique (Weintraub and Williams 1949) may be useful Barium suspension is followed up by a quantity of iced water or iced saline which accelerates the peristalsis in the small intestine so that the medium is carried to the caecum within ½–1 hour

**Method used in obscure haemorrhage**

In patients with obscure haemorrhage the method used may be the same as that used for obstructive lesions but in some cases the small bowel enema technique of Schatszki (1943) may be of value Duodenal intubation with a Ryle s or similar tube is carried out and barium sulphate suspension is injected through the tube rapidly under screen control The upper small bowel is distended to its full capacity and irregularities and defects of the lumen are clearly shown It is well not to exceed 6 fluid ounces of barium suspension in the early part of the examination otherwise filled distended loops tend to obscure each other The barium suspension can be urged on by the injection of water or saline through the tube a further quantity of opaque medium can be substituted at any stage desired The advantage of this method consists in the ability to maintain distension in the loops of small bowel being examined at will its main difficulty is that of duodenal intubation and it is not a method to be used in unselected cases

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may produce a filling defect in the greater curvature of the stomach (Scholtz 1932)

Occasionally metastases from carcinoma of the pancreas occur in association with the lower third of the oesophagus and cause dysphagia Langton and Laws (1954) have described 3 cases and collected 3 more from the literature

The possibility that a pancreatic neoplasm is responsible for an atypical dyspepsia associated with upper abdominal discomfort or pain should always be borne in mind by the examining radiologist and every effort should be made to detect abnormal displacements of the stomach and duodenum or early evidence of infiltration or disordered function which may be easily overlooked As Beeler and Kirklin (1952) have shown the site of the lesion is more contributive to its diagnosis than its mere size and small operable lesions may be recognized proportionately as often as large inoperable ones

## RADIOLOGICAL METHODS IN THE DIAGNOSIS OF SMALL BOWEL DISORDERS

*The radiological examination of the small bowel can be a lengthy procedure and* routine requests for barium meal and follow through have no justification The examination should be selective as far as possible and not incidental and the



FIG 56—Male aged 24 years 5 years history of frequent loose motions Streaks of blood in motions recently Recent loss of weight and anorexia Barium follow through 16 4 56 2 ounces of suspension used shows several constricted areas in the lower ileum where the mucosal surface is completely destroyed Diagnosis—Crohn s disease

method used should vary to show the condition likely to be present to the best advantage Information may be required concerning disturbances of function the causes of obstructive symptoms or of obscure bleeding (Fig 56)

**Barium meal in functional disturbances**

Where functional disturbances predominate as in steatorrhoea coeliac disease and chronic diarrhoeas a small barium meal of 4 ounces volume containing a

# CHAPTER 9

# THE LOWER OESOPHAGUS LINED BY COLUMNAR EPITHELIUM

N R BARRETT

THE abnormality described in this chapter has been called by a variety of names which have led to misconceptions The terms short oesophagus and congenital short oesophagus both imply that the gullet has not grown to its proper length The oesophagus lined by gastric epithelium suggests that the whole structure is so lined and that the epithelium is gastric The least misleading term is *the lower oesophagus lined by columnar epithelium* (*see* Fig 57)

## DESCRIPTION OF THE ABNORMALITY

A lower oesophagus lined by columnar epithelium is one in which a stretch of the gullet of varying length is lined by columnar and not by squamous epithelium In all other respects the parts are normal The length to which the abnormal epithelium extends upwards in a continuous sheet from the stomach varies but in most cases the change in the epithelia occurs at 20–25 centimetres from the incisor teeth in the adult

This abnormality is different from but can be complicated by a sliding hiatal hernia It is a specific entity which is comparatively rare It differs from sliding hiatal hernia because in it the external anatomy of the gullet in the mediastinum is normal there is no peritoneal sac covering one side of the herniated stomach and because the anatomy of the peritoneal ligaments the left gastric artery and the segmental aortic arteries is normal (*see* Fig 58)

There are several reasons why the lower oesophagus lined by columnar epithelium has not been recognized as an entity in the past It has been confused with sliding hiatal hernia and this has occurred because in both it appears that a part of the stomach has migrated into the posterior mediastinum In the abnormality under discussion this assumption is incorrect because it is a malformation and not an acquired hernia It is in no way related to sliding hiatal hernia in which the parts have developed normally but have subsequently assumed unnatural positions at or after birth The two also differ anatomically in the details of the pathological states which they cause and in some of the therapeutic measures which can be applied to their correction

One might have supposed that many examples would have come to the notice of pathologists who perform routine post mortem examinations but on these occasions the relevant part of the gullet is generally sliced off from the stomach before being examined and the pathologist who detects some unusual features is apt to ascribe them to post mortem changes or to *islets of ectopic gastric mucosa* This last description has been used so often and by so many people to explain abnormalities in the gullet that some statements are necessary to abolish the practice Islets of ectopic gastric mucosa exist as very small patches at all levels in the gullet but it has never been proved that they have caused a pathological lesion

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## CHAPTER 9

# THE LOWER OESOPHAGUS LINED BY COLUMNAR EPITHELIUM

N R BARRETT

THE abnormality described in this chapter has been called by a variety of names which have led to misconceptions The terms short oesophagus and congenital short oesophagus both imply that the gullet has not grown to its proper length The oesophagus lined by gastric epithelium suggests that the whole structure is so lined and that the epithelium is gastric The least misleading term is *the lower oesophagus lined by columnar epithelium* (*see* Fig 57)

## DESCRIPTION OF THE ABNORMALITY

A lower oesophagus lined by columnar epithelium is one in which a stretch of the gullet of varying length is lined by columnar and not by squamous epithelium In all other respects the parts are normal The length to which the abnormal epithelium extends upwards in a continuous sheet from the stomach varies but in most cases the change in the epithelia occurs at 20–25 centimetres from the incisor teeth in the adult

This abnormality is different from but can be complicated by a sliding hiatal hernia It is a specific entity which is comparatively rare It differs from sliding hiatal hernia because in it the external anatomy of the gullet in the mediastinum is normal there is no peritoneal sac covering one side of the herniated stomach and because the anatomy of the peritoneal ligaments the left gastric artery and the segmental aortic arteries is normal (*see* Fig 58)

There are several reasons why the lower oesophagus lined by columnar epithelium has not been recognized as an entity in the past It has been confused with sliding hiatal hernia and this has occurred because in both it appears that a part of the stomach has migrated into the posterior mediastinum In the abnormality under discussion this assumption is incorrect because it is a malformation and not an acquired hernia It is in no way related to sliding hiatal hernia in which the parts have developed normally but have subsequently assumed unnatural positions at or after birth The two also differ anatomically in the details of the pathological states which they cause and in some of the therapeutic measures which can be applied to their correction

One might have supposed that many examples would have come to the notice of pathologists who perform routine post mortem examinations but on these occasions the relevant part of the gullet is generally sliced off from the stomach before being examined and the pathologist who detects some unusual features is apt to ascribe them to post mortem changes or to *islets of ectopic gastric mucosa* This last description has been used so often and by so many people to explain abnormalities in the gullet that some statements are necessary to abolish the practice Islets of ectopic gastric mucosa exist as very small patches at all levels in the gullet but it has never been proved that they have caused a pathological lesion

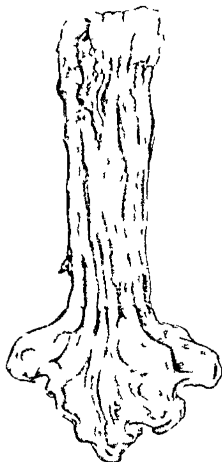


FIG 57 —Drawing of a specimen removed at operation The diaphragm the peritoneal reflections and the anatomy of the left gastric artery were normal When a barium swallow was given the patient was stated to have a normal cardiac sphincter The junction of the squamous and columnar epithelia was at the level of the azygos vein From without the oesophagus appeared to be normal There is a small columnar-cell carcinoma in the form of an ulcer at the junction of the two epithelia

(by contrast it has been proved that ectopic gastric mucosa causes haemorrhage or peptic ulceration in a Meckel s diverticulum) Nor do they explain the lesion considered in this chapter They cannot account for sliding hiatal hernia or for para oesophageal hernia They might however conceivably explain the finding of a columnar cell carcinoma *in the gullet* provided it could be shown that the tumour was everywhere surrounded by normal squamous epithelium

Every case in which columnar epithelium has been found in the lower end of the gullet (excluding those due to hiatus hernia) has come to light because a patho logical lesion was present as a complication This stresses the point that the deformity in itself may be harmless and the fact is emphasized because many of the patients develop their symptoms late in life

There has also been confusion as to the meanings of many terms used to describe the anatomy the physiology and the pathological conditions to which the gullet is heir Different authorities believing that their colleagues knew what they were talking about have used similar terms to describe different things There is for example no general agreement as to what is meant by the oesophagus To most people it is that part of the alimentary canal distal to the crico pharyngeal

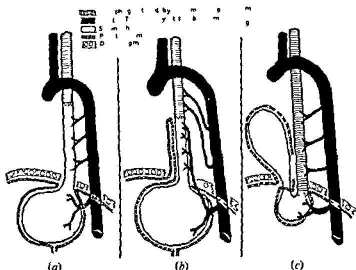


FIG 58 —Diagram illustrating the differences between (*a*) a lower oesophagus lined by columnar epithelium (*b*) a sliding hiatal hernia and (*c*) a para-oesophageal hernia The diagrams have been drawn as the parts would be seen from the left side of the chest (*By courtesy of the* Brit J Surg )

sphincter which traverses the mediastinum ends below the diaphragm at the stomach and which is lined by squamous epithelium There would be no difficulty in accepting this definition were it not that in the cases here described a varying length of the lower part of the oesophagus is lined by epithelium which macroscopically resembles that in the upper part of the stomach It is for this reason that some prefer to use the term gullet which is derived from Middle English and defined in the *Oxford English Dictionary* as the passage by which food and drink pass from the mouth to the stomach Such a term is helpfully non-committal the gullet ends where it joins the bag of the stomach

Another doubt centres around the term cardia In a normal man this is used to describe three points (1) where the gullet enters the stomach (2) where the mucous membrane changes from squamous to columnar and (3) where the valve mechanism (to prevent reflux of gastric contents) is situated These three occur normally at the same level and constitute the cardia To which therefore does the term refer if the valve mechanism lies at a different level to the place at which the mucous membrane changes? There are advantages in confining the word cardia to describe only the valve mechanism and not the mucosal junction which can be several inches higher up in the gullet In this chapter the cardia is the valve between the gullet and the stomach

## AETIOLOGY

There are a variety of ways in which one may attempt to explain the appearance of columnar epithelium at the lower end of the gullet and three of these will be examined briefly

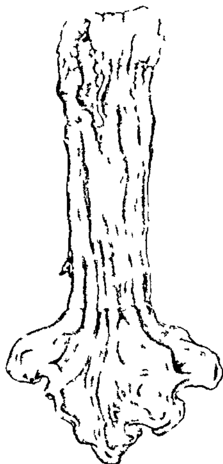


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typical gastric mucous membrane oxyntic cells appear and increase in numbers and near the junction of the gullet and the stomach the glands become deep and complicated At any point in this columnar epithelium islets of perfectly developed squamous epithelium can often be seen

These findings suggest that although the epithelium which lines the lower part of the gullet in these cases makes the part look like an upward extension of the stomach this is not the real explanation for beyond the fact that the misplaced epithelium is columnar in type the greater part of it has not the characters of secreting gastric mucosa

**Embryology**

Until recently differences of opinion have existed as to the development of the oesophageal epithelium and of its glands in man To elucidate these problems transverse sections of human embryos at all stages in development between 3 and 230 millimetres C R lengths were cut by Johns (1952)

From the 3 millimetre until the 16 millimetre stage the epithelium from one end of the gullet to the other is stratified columnar in type

Between the 23 millimetre and 34 millimetre stages it becomes two layered and subsequently changes to multi layered although the cells remain columnar This epithelium proliferates to such an extent that the lumen of the oesophagus is actually or nearly obliterated and the channel is ultimately re established by vacuolation The vacuoles are largest above the level of the tracheal bifurcation and persist until the embryo is about 70 millimetres in length Similar vacuolation occurs in the embryonic oesophagus of the pig the rabbit the rat and the hedgehog

After the 70 millimetre stage islets of ciliated columnar epithelium which arise from the basal layer of the preceding stratified columnar lining appear in the middle of the gullet they extend coalesce and ultimately line the whole tube

In the 130 millimetre embryo the ciliated columnar lining has been replaced by stratified squamous epithelium and this change also begins in the middle reach of the oesophagus and extends upwards and downwards The last segment to lose its ciliated columnar epithelium is the upper end of the gullet and traces of these cells have been described as persisting at birth

During the development of a human embryo the sequence of changes in the epithelia which line the foregut might be arrested or deviated from normal Thus it is not surprising to find columnar ciliated transitional or squamous epithelium anywhere between the mouth and the duodenum

In the light of this evidence it is misleading to describe the lesion under discussion as a congenital short oesophagus because this suggests that the oesophagus has not grown to its accustomed length In fact in these cases the anatomy of the gullet and of the stomach is normal in every respect except one namely that the full sequence of changes which should have occurred in the mucous membrane of the oesophagus have not reached fruition and the result of this failure is that the lower section of the gullet looks as though it is lined by gastric epithelium Histologically it is lined by mucus secreting columnar cells and in the vicinity of the cardia there are some oxyntic cells which could predispose the patient to peptic ulceration

Thought in these cases has been influenced by the idea that in the human embryo the stomach and the gullet are different viscera In fact they develop as

**Comparative anatomy**

A study of the various types of epithelia which line the gullets in vertebrates shows that the arrangement in man is special and peculiar It is only in some of the carnivora and the apes that the epithelium changes abruptly from squamous to columnar precisely at the cardiac valve There is no evidence that in most vertebrates the secretions of the stomach are harmful to the squamous cells which line the gullet and in consequence a cardiac sphincter to protect against reflux is an unnecessary luxury and would hinder such activities as rumination Thus the precise limit of this or that epithelium is not crucial in most animals and considering our zoological ancestors it should not surprise us if we harbour variations in the gullet from time to time But the condition which has been called short oesophagus is peculiar even in the light of the above remarks because in it columnar epithelium is found reaching in a continuous sheet *above* the oesophago-gastric junction and this does not happen naturally in the lower vertebrates It appears to be a unique deformity Moreover the opposite state namely an extension of the squamous epithelium of the gullet down into the viscus called the stomach does not happen in man but is a common arrangement in other vertebrates In animals as widely different as the horse the ox the rabbit and the rat the squamous epithelium of the gullet passes down below the anatomical cardia and fanning out lines a large part of the stomach The viscus called the stomach in many of these animals is composed of two or more sacs which communicate with each other and between these sacs there is no passive barrier or active sphincter The proximal sacs which are lined by horny squamous epithelium function as reservoirs for the food and only the distal sac or true stomach is concerned with the preliminary digestion of protein The whole of the stomach in the duck billed platypus is lined by squamous cells

Thus the columnar epithelium which lines the lower part of the gullet in short oesophagus cannot be accounted for as a reversion to a more primitive zoological state because in the majority of mammals the junction of the squamous and columnar epithelia lies beyond the cardia and this arrangement has not as yet been described in man

**Histology**

If a specimen removed at operation is examined the upper end of the gullet appears to the naked eye to be lined by squamous epithelium and the lower end looks like stomach The columnar epithelium is bluish in colour voluminous and raised in rugae

Histologically the proximal part of such a specimen is typical squamous epithelium and the transition between it and the lower epithelium is abrupt Just below this boundary the columnar cells are arranged as simple shallow tubular glands amongst which lie numerous mucus secreting cells (Figs 59 60 and 61) In this upper region which appears macroscopically like stomach there are no oxyntic cells and the epithelium is similar to that which forms the deep mucous glands of the normal oesophagus If it were not for the fact that the deep oesophageal glands appear after birth one might be tempted to assume that the columnar epithelium in these cases is the result of an overgrowth of the normal oesophageal gland epithelium which had as it were spread out over the surface and covered it

Lower in the gullet the simple tubular crypts gradually give place to more

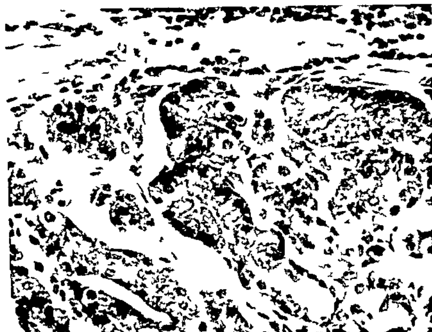


FIG 61 —Microphotograph showing oxyntic cells in the columnar epithelium which lined a gullet and which lay above the cardia The patient had the lower part of the gullet removed because a stricture had developed at the junction of the squamous and columnar epithelia above the level at which this section was made

one tube which differentiates into its adult components late in the growth of the embryo In the complicated evolutions which occur to this end the parts could become anatomically unusual by failing to achieve normal maturity

The above ideas do not smooth away all difficulties If they be true why for example does the abnormality always occur at the lower end of the gullet? Surely there would be occasions when the upper end might be lined by columnar and the lower by squamous epithelium Why is the human stomach never lined by squamous cells and why do gastric ulcers occur in the abnormal parts? Until these discrepancies can be explained one must at least concede that in some cases there is a failure in the longitudinal growth of the oesophagus and that this results in the presence of a partial thoracic stomach

## PATHOLOGICAL CHANGES

Surgeons who have studied the histology of specimens removed at operation have found that the greater part of the unusual epithelium consists of simple tubular glands which secrete mucus but which include few true gastric elements There are oxyntic cells at the lower end of most specimens and these may be situated proximal to the junction between the gullet and the stomach Thus the abnormal segment may never be subjected to the harmful effects of gastric juice but in speculating about this point there are other factors concerned



FIG 59 —Microphotograph of the wall of the gullet in a patient who had the lower part lined by columnar epithelium *Note the simple columnar glands which are* not like those found in the stomach This preparation was made from the top of *the specimen near to the junction of the two epithelia*



FIG 60 —Microphotograph from the lower part of the same specimen as that shown in Fig 59 Note that the glands are becoming more complicated and that there is an islet of squamous epithelium among the columnar glands One could not describe the epithelium in either of these slides as gastric epithelium

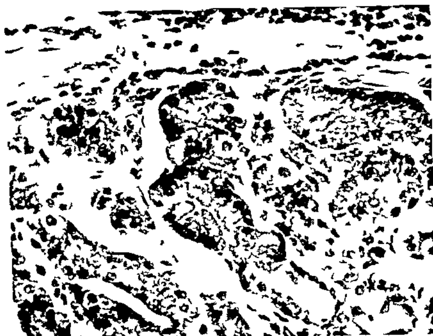


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The junction between the squamous and columnar epithelia in these cases is generally situated at about 20–25 centimetres from the incisor teeth and not just above the diaphragm as it is in most sliding hiatal herniae and it has often been stated that the higher up the gullet the less the risk that the squamous epithelium will be digested A good reason for this statement has not been given by those who make it but it has been suggested that the upper parts are better protected by mucous and saliva

Is there in these patients a *cardiac valve mechanism and if so where is it situated?* My observations suggest that two types of case occur The first is the patient who has the lower part of the gullet lined by columnar epithelium and no pathological lesion at the cardia On a barium swallow and when examined *radiologically this individual has what appears to be a normal gullet the cardiac* valve is in its usual place and the mechanism does not permit reflux That is the cardiac valve is some way distal to the level at which the change over in the epithelium occurs and between the valve and the change over there is a segment of *gullet lined by abnormal epithelium* The fact that a cardiac valve can function normally in such cases indicates that the exact histology of the epithelium at the level of the valve is not in itself important in its action

The second is that described by Allison and Johnstone (1953) who reported that in most of their patients the lesion was complicated by the presence of a typical sliding hiatal hernia below the abnormal mucous membrane In these there was no cardiac valve and free reflux of gastric contents was usual In the past these cases have been diagnosed as straightforward examples of sliding hiatal hernia In both types a variety of different lesions can occur singly or in combination

**Reflux oesophagitis**

Oesophagitis may be initiated by reflux of gastric contents or as a result of secretions from the cells which line the pouch It could also be due to both factors operating simultaneously

The various pathological changes which have been found follow the pattern described by Allison and Johnstone (1953) The lesions may be superficial and transient involving only the squamous epithelium or they may be permanent and take the form of shallow ulcers and leucoplakia The ulcers are generally situated at the point where the squamous epithelium ends and the lower margin of the defect abuts upon the columnar epithelium Ulcers which are due to oesophagitis do not perforate or cause massive bleeding by eroding a large blood vessel they can however cause anaemia because of a persistent small loss of blood In some circumstances the inflammation may spread more deeply than the mucous membrane and if it persists a stricture results

Oesophageal strictures in these cases occur in several varieties In some the fibrous tissue which encircles the gullet remains as a narrow ring like band—these are the strictures which Allison says can be excised locally by splitting the muscle coats removing the ring of scar and leaving the mucous membrane intact In others the fibrous tissue invades and destroys the muscle coats and forms a palpable hard tumour of considerable size This fibrous tumour becomes adherent to the adjacent structures in the mediastinum and is difficult to dissect free It is easy to mistake such a lesion for a malignant growth and some of the cases of supposed carcinoma which have been treated palliatively and survived are probably

in this category In yet other strictures there is a local accretion of tissue which forms an obvious lump and which histologically is found to be mainly hyper trophied muscle fibres Such specimens when split longitudinally may have the appearance of the pylorus in a case of congenital stenosis The explanation of these findings is not clear

**Peptic ulcer**

Cases have been described of patients who have developed peptic ulcers in the abnormal segment of the gullet These ulcers have nothing in common with the oesophageal ulcers described above they occur at a level below the change over in the mucous membrane and they behave as do gastric ulcers in the stomach Two kinds of peptic ulcer have been found

*Acute peptic ulcers*

These are not uncommon It may be that these erosions are the result of post mortem changes in some instances but they are often real ulcers Their presence could account for some cases of unexplained haematemesis Allison and Johnstone (1953) have raised another interesting point it is not known whether such an ulcer would heal by covering of columnar epithelium it might heal by squamous metaplasia and if so could account for the islets of squamous epithelium which have been found amongst the columnar cells in these cases Such a speculation emphasizes the ever recurring question as to which lesions of the gullet are acquired and which are congenital

*Chronic peptic ulcers*

Since the time of Rokitanski chronic peptic ulcers have been described as occurring in the oesophagus but the issue has been confused because it used to be stated that they had arisen in isolated patches of ectopic gastric mucous mem brane This is not true

The differences between these ulcers and oesophageal ulcers on the one hand and gastric ulcers on the other were first emphasized by Barrett (1950) and for this reason the chronic peptic ulcer which complicates the lesion under discussion and which is situated in what appears to be the gullet has been referred to in the literature as Barrett s ulcer

Barrett s ulcers resemble chronic gastric ulcers (Figs 62 and 63) They generally occur in middle aged or elderly people and they invade and destroy the muscle coats of the gullet The adjacent tissues are oedematous in life and as the ulcer penetrates through the wall of the gullet the mediastinal tissues become involved by fibrosis and inflammatory adenitis The ulcer is liable to produce haemorrhage (by perforating a large blood vessel) or mediastinal and pleural suppurations Malignant change has also been described as having originated in such an ulcer but the evidence is not conclusive

The risk of a stricture forming is not great because these ulcers grow in the line of the gullet and seldom involve the whole circumference Thus the fairway is not usually obstructed and dysphagia of which the patient may complain is generally due to spasm above the lesion and to local oedema One may generalize and say that a benign stricture discovered in the lowest part of the gullet is not likely to be due to a Barrett s ulcer On the other hand a stricture demonstrated at or above the aortic arch is almost certainly situated in the squamous epithelium

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FIG 62 —Specimen removed at autopsy by Professor Barnard showing a typical chronic gastric ulcer which has perforated into one of th pulmonary veins and caused death from haemorrhage At the top of the specimen is the larynx and the gullet has been transected about 2 inches below the aortic arch The junction of the columnar and squamous epithelia is $1\frac{1}{2}$ inches above the ulcer which is everywhere surrounded by columnar epithelium Note that no stricture has formed at the site of the ulcer and that there are genuine patches of ectopic gastric epithelium in that part of the gullet lined by squamous epithelium at the top of the specimen (*By courtesy of the Editor of* Brit J Surg )

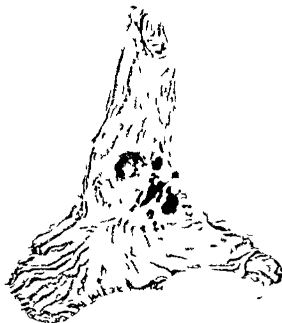


FIG 63 —Drawing of a specimen removed at autopsy showing a typical chronic gastric ulcer which was adherent to the aorta and which was situated in the mediastinum The lower 3 inches of the gullet were lined by columnar epithelium and the junction between this and the normal squamous epithelium of the oesophagus is depicted at the top of the specimen In addition to the chronic peptic ulcer there are several acute ulcers in the vicinity which could be post mortem artefacts (*By courtesy of the Editor of* Brit J Surg )

above a lower oesophagus lined by columnar epithelium Allison and Johnstone (1953) have had experience of 115 patients suffering from stenosis due to oesophageal ulcer (that is ulcer in the squamous epithelium) and 10 others with stenosis due to Barrett s ulcer In these 115 patients there was indisputable evidence of a segment of oesophagus lined with gastric mucosa between the stenosis and the (hiatus) hernia below They concluded that the relative chances of a peptic stenosis of the gullet being oesophageal or gastric is about 10 to 1 in favour of the former

## Carcinoma

Carcinoma occurs (Fig 57) both at the level of the change over in the mucous membranes in which case it is squamous in type and in the lower part of the gullet when it is columnar There are no special features which distinguish these lesions from those growing in the normal gullet or stomach but one important



FIG 64 —Photograph of a specimen removed at operation It was diagnosed as a columnar cell carcinoma at the cardia In fact the whole of the mucous membrane of the gullet in this specimen is columnar in type and in consequence this is a columnar-cell carcinoma of the gullet

misconception needs correction If a carcinoma develops at the anatomical oesophago gastric junction and if it is columnar it is difficult to say whether it has originated in an abnormality of the type under discussion in this chapter or whether it is an example of an upward extension of a gastric cancer into the gullet (Fig 64) The point is of academic interest at the level of the diaphragm but if a columnar cell growth is discovered at the level of the arch of the aorta how is one to interpret this finding? In the past it has been said that the inference in such a case is that a gastric cancer has grown up the gullet from the level of the diaphragm If this were always true the prognosis as regards resection would be hopeless because of the extent of the tumour but it is not always true The usual explanation of such a finding is that the patient has developed a columnar cell cancer *de novo* in a stretch of abnormal oesophageal mucosa and some of these cancers are localized and favourable for resection The explanation that a columnar growth could have originated in an oesophageal mucous gland is possible but has not

been substantiated by an actual specimen To prove this point would involve demonstrating a columnar cell cancer entirely surrounded by squamous epithelium

## DIAGNOSIS

When the lower part of the gullet is lined by columnar epithelium the patient will have no signs or symptoms unless a pathological lesion is present In such a case a barium swallow would not reveal an abnormality either in the part which is assumed to be normal gullet or in the stomach That is the columnar epithelium in the lower part of the gullet does not affect normal peristalsis or cast a typical shadow of rugae

The diagnosis will be made only when a pathological process has been added to the abnormality of development As described above the pathological changes which are relevant are oesophagitis oesophageal ulcer oesophageal stricture Barrett s ulcer and carcinoma

### Symptoms

The symptoms of oesophagitis and its complications are the same as those which occur when this process is due to a sliding hiatal hernia except that the pain is often felt higher in the thorax and referred to the middle of the sternum Dysphagia and regurgitation of food and saliva with mucus are common and anaemia due to slow bleeding is a feature

The symptoms due to Barrett s ulcer or to its complications are not specific but the pain is more likely to be related to the taking of food than to the effects of posture These patients may complain of a severe boring pain localized to the back if fixation to the aorta is occurring If on the other hand there is a perforation into the mediastinum the signs and symptoms exactly mimic those which are generally regarded as characteristic of a perforated gastric ulcer in the peritoneal cavity The author has had experience of a case in which the ulcer caused at first a pericardial effusion and later death due to suppurative pericarditis If a major blood vessel such as the aorta is eroded the patient will die of massive haemor rhage Loss of weight is a common complaint and symptoms such as dysphagia are often of long duration There may be periods of remission in which it is possible that a measure of healing has occurred or spasm and oedema may have subsided for the time being In the first series of cases which the author published (Barrett 1950) the patients had all died as a result of the complications caused by their ulcers None had been diagnosed correctly or treated in life

### Radiological findings

Johnstone (1953) has described the radiological findings when the lower oeso phagus is lined by columnar epithelium He has emphasized that unless a patho logical lesion is present in the gullet there is no special pattern caused by the columnar mucosal folds which suggests the diagnosis the superficial lesions due to oesophagitis cannot be seen and peristalsis is not abnormal A benign stricture at the level of the aortic arch should suggest that the lower oesophagus is lined by columnar epithelium because sliding hiatal hernias are not as large as this

The cardiac sphincter in these cases will be incompetent if a hiatal hernia is also present but if not there will probably be a mechanism which prevents reflux situated at the expected place that is below the diaphragm where the gullet appears

to enter the stomach These cases lend support to the proposition that the most important single factor in competence or otherwise of the cardiac valve mechanism is the angle at which the gullet enters the stomach The writer has had 2 patients who in spite of symptoms were at first thought to have nothing abnormal because a competent cardia was seen in the usual place below the diaphragm Both had gullets lined with columnar epithelium and oesophagitis at the level of the aortic arch

If a Barrett s ulcer is present in the lower part of the gullet Johnstone (1953) believes that a correct diagnosis can generally be made if a barium swallow is given He says When a *deep* ulcer crater can be demonstrated close to the cardia there is strong presumptive evidence of its gastric origin Such craters may be more than a centimetre in diameter The walls are clear-cut and in one case terracing was observed Undermining of the margins has also been seen but the edges appear regular and smooth The crater is usually single but in two instances a second crater has been found They are more often on the posterior or the postero lateral wall and they tend to spread longitudinally rather than to encircle the lumen In some the crater lies in the stenotic segment but in others the lumen is scarcely narrowed and there is little obstruction Peri oesophageal infiltration is not uncommon and soft tissue shadows may be seen at the base of the ulcer It is not possible to distinguish radiologically between such an ulcer and a carcinoma which is the more common lesion

**Oesophagoscopy**

Oesophagoscopy is an essential pre operative investigation in all patients suffering from diseases in the gullet

In these cases the diagnosis should always be suspected if the change over of the mucous membrane is found at a high level As the epithelial transition is sharp there should be no difficulty in marking its point unless there is local inflammation if there is a doubt pinch biopsies will settle the matter In most of the author s cases the change has been at about 25 centimetres from the incisor teeth and this is higher than one expects it to be if the diagnosis is a sliding hiatal hernia

A fact which suggests that the lower part of the gullet is lined by columnar epithelium is that the level at which the change over of the epithelium occurs at endoscopy does not tally radiologically with the observed level of the cardiac valve mechanism

A point which clinches the diagnosis is that columnar epithelium is found above a pathological lesion in the gullet If the patient has a stricture at the oesophago gastric junction the radiologist is likely to call it a carcinoma and the fixity of the parts may suggest the same mistake to the endoscopist even though a negative biopsy has been obtained The moral of this is that if a good piece of tissue has been obtained for biopsy and if the histological report is against carcinoma the possibility of a benign stricture should be entertained Such strictures occur

The diagnosis of Barrett s ulcer at endoscopy is difficult not only because these ulcers sometimes exist beyond an oesophageal stricture but because through an oesophagoscope they look like carcinoma There is obvious *piling up of tissue* at the edge of the ulcers and necrosis in the floor These factors spell carcinoma of the gullet to most surgeons

**Thoracotomy**

In some cases the diagnosis will not be confirmed until the structures in the lower mediastinum and in relation to the right crus of the diaphragm which

been substantiated by an actual specimen To prove this point would involve demonstrating a columnar cell cancer entirely surrounded by squamous epithelium

## DIAGNOSIS

When the lower part of the gullet is lined by columnar epithelium the patient will have no signs or symptoms unless a pathological lesion is present In such a case a barium swallow would not reveal an abnormality either in the part which is assumed to be normal gullet or in the stomach That is the columnar epithelium in the lower part of the gullet does not affect normal peristalsis or cast a typical shadow of rugae

The diagnosis will be made only when a pathological process has been added to the abnormality of development As described above the pathological changes which are relevant are oesophagitis oesophageal ulcer oesophageal stricture Barrett s ulcer and carcinoma

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The cardiac sphincter in these cases will be incompetent if a hiatal hernia is also present but if not there will probably be a mechanism which prevents reflux situated at the expected place that is below the diaphragm where the gullet appears

Barrett s ulcer is present the mediastinum will be distorted by dense adhesions and adenitis

(2) Although the lower part of the gullet is lined by columnar epithelium this may secrete so little digestive ferment as to be harmless Such ferments as it does produce may be neutralized by saliva and their effects counteracted by protective mucus

(3) A valve like mechanism often exists at the anatomical junction of the gullet and the stomach that is below the change-over in the epithelia This valve could also shut off the secretions from the stomach proper Thus it is of more than theoretical interest to know if a valve exists in a specific case

(4) If it is necessary to excise the abnormal segment of the gullet there are a variety of ways in which the continuity of the alimentary canal can be restored On the whole it is objectionable to anastomose the proximal part of the oesophagus directly to the stomach because such a procedure merely sets the stage for further complications If the surgeon wishes at all costs to avoid short-circuiting the stomach he may elect to do a partial gastrectomy and pyloroplasty as advocated by Wangensteen (1949) or the operation described by Ellis (1956) in which the offending part of the oesophagus is taken away together with the pre pyloric part of the stomach Allison (1953) has advocated oesophago jejunostomy and more recently oesophago jejuno gastrostomy The latter has been popularized in the United States of America by Merendino (1955) but has been used for a number of years in Great Britain In a personal communication Brain tells me that he now interposes the isolated ileo-caecal junction between the oesophagus and the stomach hoping in this way not only to keep the stomach in the main passage of the food but to prevent gastric reflux

Various contingencies arise some of which will be discussed

(1) The patient complains of heartburn and on investigation has a normal barium swallow and no oesophagitis at oesophagoscopy but the lower oesophagus is lined by columnar epithelium

In such circumstances one may assume that the secretions from the lower part of the gullet are harmless and that the heartburn was due to intermittent reflux from the stomach If medical measures did not produce relief the object of performing an operation would be to improve the competence of the cardiac mechanism and the presence of the abnormal epithelium in the gullet could be ignored Thus some operation designed to accentuate the oesophago gastric angle might be tried

(2) The patient complains of heartburn and has oesophagitis above a stretch of gullet lined by columnar cells

This could be due to reflux of secretions from the stomach or to an unusually large number of oxyntic cells in the abnormal epithelium of the gullet Hence if an operation is to be performed the lower end of the gullet must be separated from the zone of oesophagitis In practice this means resecting the gullet between the inflamed area of squamous epithelium and the stomach The chief difficulty of this operation is to know how best to reconstitute the alimentary canal

(3) The patient has dysphagia due to a benign stricture at the change over of the epithelia

The choice lies between repeated endoscopic dilatations followed by medical treatment local excision of the stricture (either by Allison s technique or by excision with end to-end anastomosis of the gullet) or excision of the stricture and of the lower part of the gullet with reconstruction of the alimentary canal All these operations are difficult

forms the oesophageal hiatus can be inspected at thoracotomy The presence or absence of a peritoneal sac the anatomy of the hiatus and of the left gastric artery are the deciding factors

## THE IMPORTANCE OF AN ACCURATE DIAGNOSIS

It is reasonable to inquire what is the practical value of being able to distinguish between a gullet partially lined by columnar epithelium and a sliding hiatal hernia Both seem to produce similar diseases and all one need know is that there are two conditions which may be different in origin but which result in the same defects It is possible to make a case against this argument thus

(1) In sliding hiatal hernia the abnormal segment is a part of the true stomach in this condition it is neither true stomach nor oesophagus How it may behave physiologically and pathologically is impossible to predict

(2) When the lower part of the gullet is lined by columnar epithelium the cardiac valve (if one exists) lies beyond the point where the epithelia change After a sliding hiatal hernia has been reduced the cardiac valve and the change over in the epithelia correspond in level

(3) In sliding hiatal hernia competence of the cardiac valve is attained by restoring the parts to their normal anatomical positions Symptoms due to the abnormality under consideration can seldom be cured in this simple way because there is no hernia to reduce and because the inflammation in the gullet is not always due to incompetence at the cardia

(4) The strictures which occur as a result of the lower gullet being lined with columnar epithelium are generally situated higher in the mediastinum than those due to a sliding hiatal hernia This increases the technical difficulties of reconstituting the alimentary canal after excision

(5) Barrett s ulcer is rare as a complication of sliding hiatal hernia (but peptic ulcers occur in para oesophageal or rolling hernias) It is relatively common if the lower part of the gullet is lined by columnar epithelum and its presence raises difficult problems of treatment

(6) It is probable that the majority of columnar cell carcinomas arising in the gullet (as opposed to the cardiac end of the stomach) grow from a segment whose lining is abnormal The treatment of cases of this type has not been specifically considered by surgeons as yet The prognosis in relation to radiotherapy and excision may not be the same as it is when the growth is squamous or truly gastric in origin

## TREATMENT

The lower oesophagus lined by columnar epithelium has not been recognized long enough for anybody to be dogmatic about treatment The following observations represent ideas rather than techniques of proved value

Some of the patients can be controlled by conservative treatment and since the alternatives are drastic this should be tried at first If a stricture is present and the diagnosis has been established it may be permissible to dilate the stricture through an oesophagoscope and persist with medical measures this applies especially to elderly patients

Before contemplating a major surgical operation the following points must be remembered

(1) The anatomy of the gullet the stomach the peritoneum and of the gastro oesophageal ligaments is normal There is no hernia to reduce If a stricture or a

## CHAPTER 10

# THE REGULATION OF GASTRIC EMPTYING

J N Hunt

## INTRODUCTION

Once a man has chosen tasted and chewed his food and begun to swallow it the bolus slips suddenly into the grip of a chain of reflexes from which there is normally no return (Cannon 1911) If all goes well there is no awareness of digestive activity except a sense of satisfaction Any other form of sensation arising during digestion may be regarded as dyspepsia which is the point of view of many patients who complain for example of wind gurglings splashings fullness and nausea but not necessarily of pain Derangements of gastric emptying are potent causes of dyspepsia unduly rapid emptying may give rise to griping sometimes followed by a purge unduly slow emptying is often associated with a sense of fullness and loss of appetite In some instances these symptoms are not primarily the result of a gastric disorder but depend rather upon an ill choice of food or upon a low threshold for dyspepsia in the central perceptive mechanism

No one can be considered immune from dyspepsia but certainly in some people the alimentary tract seems to tolerate several severe simultaneous insults any one of which in a mild degree would give rise to dyspepsia in others Such sensitive persons may be said to have a low eupeptic reserve somewhat analogous to a low cardiac or respiratory reserve

Dyspeptic patients can sometimes be helped by taking a careful history and providing some alterations of regime based on a knowledge of the physiology of the receptors concerned

Knowledge of the factors which operate alimentary mechanisms may be of importance in another context In severe illness the patient is sometimes denied all choice of food and special mixtures are fed by tube Consideration of the caloric content and of the end products of metabolism of such mixtures must be harmonized with the requirements of alimentary comfort For obstetricians the knowledge that solutions of glucose if concentrated leave the stomach slowly may actually be life saving in preventing inhalation of vomit during anaesthesia in labour

In this chapter it is intended to discuss the mechanism of gastric emptying and its regulation by receptors in the upper alimentary tract

## GENERAL PRINCIPLES

Gastric emptying is arranged in such a way that the stomach transfers its contents to the intestine as quickly as possible without injury to the absorbing mechanism and without overwhelming the storage tissues

### Intestinal protection

The regulation of gastric emptying can be most easily understood in terms of an interplay between three guiding principles The lining of the stomach is more

(4) The patient has a Barrett s ulcer

Surgical treatment is essential in most of these cases but not before every effort to establish temporary healing has been made Bed rest and a jejunostomy for feeding are the best preliminaries These ulcers probably behave like gastric ulcers and some can be induced to heal As they heal the oedema in the surrounding tissues subsides and a patient who has complained of dysphagia may swallow again To operate before taking these precautions is to invite technical difficulties There is no information as to whether an ulcer which has healed will remain quiescent and the general feeling at the moment is that it should be removed To achieve this the lower part of the gullet must be mobilized and the mass of inflammatory tissue around the ulcer itself makes this step difficult and sometimes dangerous Before dissecting the gullet away from the aorta the latter should be separated above and below the level of the ulcer so that it can be temporarily clamped off if serious bleeding should occur Having dissected the gullet free the lower part containing the abnormal epithelium and the ulcer must be excised and the continuity of the alimentary canal restored

(5) The patient has a combination of pathological lesions

In these circumstances there will seldom be any alternative but to resect the whole of the abnormal area if a sliding hiatal hernia is also present it must be reduced in order to achieve a competent cardia or excised with the lower part of the gullet

(6) The patient has a columnar cell carcinoma in the gullet

If the growth be situated at the lower end and in proximity to the stomach the treatment will be resection and some type of anastomosis In many cases the most the surgeon can offer is that he can so arrange matters that the patient can swallow There is no justification in the author s opinion in opening the chest in such a case finding the growth to be inoperable and saying nothing can be done Whatever is found the patient s dysphagia must be cured This at least can be done in practically every case

If the carcinoma is at the level of the aortic arch or higher there is less experience to draw upon Two points suggest themselves It may be that some of these cases will respond to radiotherapy better than one hopes and this kind of treatment could be a valuable preliminary to surgical excision Such problems have been reviewed by Smithers (1956 1957) The other point is a surgical one what should one excise? The whole of the lower oesophagus and most of the stomach and its mesenteries or more simply the growth and the tissues in its immediate neighbourhood? Either operation could involve plastic procedures such as reconstruction of a bronchus and perhaps replacement of a segment of the gullet by a suitable graft

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seen radiologically to pass along the gastric axis—there is little doubt that peri stalsis is responsible for the main part of the transfer of the gastric contents to the duodenum

## FUNCTIONAL SIGNIFICANCE OF THE SHAPE OF THE STOMACH

### Tension of the stomach wall

Cannon (1911) drew attention to the importance of the shape of the stomach in determining the site of origin of gastric peristaltic waves He postulated that a particular tension was necessary to stimulate gastric smooth muscle to contract rhythmically A tension less than threshold had no effect and a tension greater than the effective tension made the muscle refractory

It may be shown by simple physical experiments that the tension in the wall of a cylinder increases as the radius of the cylinder increases if the contents remain at constant pressure The examination of a balloon at its maximal circumference and at its neck will clarify this point

If a full stomach were to be straightened out it would have roughly the form of an inverted cone with the result that the radius of a horizontal cross section and consequently the tension in the circumferential fibres will be greater in the fundus than in the antrum It might be supposed therefore that giving a meal of very large volume would so distend the stomach that the tension in the circumferential fibres would exceed the tension required to promote peristalsis in all except the fibres of the antrum where the radius is minimal and that peristalsis would be confined to the antrum As the stomach empties the site of origin of the peristaltic waves should gradually move towards the fundus only to be displaced towards the pylorus when a further volume of meal was taken Much of this was observed by Cannon (1911) in cats with the spinal cord destroyed and Hills and Hunt (unpublished) have confirmed these findings in a few students using meals of 1 250 millilitres of barium suspension

### Effects of distension

Cannon (1911) noted that distension of the stomach with a meal caused the onset of peristalsis but this took place only when the muscle was in a state of tone and resisted the distension Distension of the flaccid stomach did not promote peristalsis When an anaesthetized cat with intact vagi was given a meal peristalsis began within a minute or two If the vagi were cut at this stage emptying was unaffected and proceeded normally but if the vagi were cut before the meal was introduced then emptying took much longer to become established It is perhaps relevant that Douthwaite and Thorne (1951) who gave hexamethonium bromide to patients with duodenal ulcers—a measure which might be regarded as a pharma cological acute vagotomy—noted that the time required for gastric emptying to be established was increased in a significant proportion of their subjects It seems reasonable to suppose that impulses in some vagal fibres adjust the tone of the stomach to the volume of the meal ingested with the result that the tension of the gastric smooth muscle is suitable for the initiation of its peristalsis Reflex effects on gastric motility have been produced by stimulating the central end of the vagus in cats (Harper et al 1956) and Paintal (1954) has described the characteristics of gastric stretch receptors which might initiate such reflexes

robust than the duodenal jejunal and ileal mucosa which is functionally and structurally deranged even by distilled water (Dennis 1940 Blickenstaff 1954) A very slow rate of gastric emptying will provide a minimal stress on the intestinal mucosa since it allows adequate time for dilution by secretion in the lumen

**Smoothed absorption**

Alimentary function is so arranged that the liver pancreas and the storing tissues are not usually overwhelmed by a sudden rise in the concentration of digestive products in the blood For example if large amounts of carbohydrates are suddenly run into the gut they may so raise the blood sugar that it exceeds the renal threshold and sugar is lost in the urine The stomach contributes to this principle in that gastric transfer of concentrated solutions of foodstuffs into the gut is slower than that of dilute solutions

These two principles—that of intestinal protection and that of smoothed absorption—are mediated by the regulation of gastric emptying

**The law of Marbaix**

An antagonistic principle which must also be considered is the law of Marbaix (1898) that the rate of emptying of the stomach is proportional to its distension

These three principles govern the rate of presentation of material to the intestine in terms of an integration of the volume the concentration and the nature of the gastric contents

**Gastric emptying**

Under the heading of reservoir function of the stomach it is important to clear away a misconception which appears to be widespread The stomach does not *receive food digest it and after a period begin to present it to the small intestine* Gastric emptying normally begins within a few minutes of gastric filling (McClure et al 1920) Thus at the cost of some food receiving almost no gastric digestion the small intestine is quickly set to work digesting and absorbing There is evidence of this in the rise in the level of glucose in the blood which occurs within a few minutes of the ingestion of solutions of sucrose

**Composition of the chyme**

The composition of the material which the stomach transfers to the duodenum probably varies as gastric digestion proceeds and as the stomach adds acid and pepsin to the meal This view might be disputed on the ground that gastric digestion *mainly involves only the surface of the gastric contents* which is in contact with the *gastric mucosa so that peristaltic stripping of* digesting material from a solid core would minimize the change in compositon of the chyme This is true of the rat (Grutzner 1905) but in man the gastric contents are usually too liquid to satisfy any hypothesis depending upon a solid central core of food

## PROPULSIVE MECHANISM OF THE STOMACH

**Peristalsis**

Although gastric emptying may occur in the apparent absence of peristalsis (Barclay 1936 Shay and Gershon Cohen 1934)—that is a wave of constriction

**Regulation by the antrum the pylorus and the bulb**

There are two possible schools of thought on the final method of regulation of the gastroduodenal pump On the one hand the pylorus may be regarded as the sole regulator so that vigorous peristalsis continues unabated against varying degrees of resistance of the pylorus on the other the antrum pylorus and bulb may be regarded as a single functional unit with the activity of the component parts varying in a co ordinated manner The majority of the evidence obtained from dogs is in favour of the second hypothesis but under some circumstances in man the pylorus does appear to be resisting successfully the powerful propulsive activity of the antrum Furthermore the duodenum has been demonstrated to have a faster rhythm than the stomach Not only do different techniques give different results but investigators very properly give the most weight to the phenomena which they see most frequently Clinicians see different patients every day for each patient the examination is a significant event giving rise to some anxiety Those who work with dogs have 4 or 5 dogs which usually compete for the attention of the examination and are often examined 50 or more times It is not surprising that the results of these various studies differ On the other hand when test meal studies of man are made in the laboratory it is remarkable that successive experiments including the first give very similar rates of emptying in each subject It must be supposed that a given emptying can be achieved in a variety of ways and that it is emptying which is reproducible but the mode of emptying which is variable

## THE PATTERN OF GASTRIC EMPTYING

From studies with test meals it is known that the stomach has a definite pattern of emptying an example of which is shown in Fig 65 On the ordinate is given the volume of the original meal remaining at times shown on the abscissa These data were obtained by giving 19 subjects 190 standard test meals of 750 millilitres (Hunt and Spurrell 1951) The gastric contents were withdrawn after varying periods on different days From the amount of dye remaining in the stomach the volume of original meal remaining was calculated From the shape of the regular curve in the figure it may be seen that emptying of the meal becomes progressively and regularly slower as time passes As two thirds of the results of these serial test meals fell within the area outlined by the broken lines it may be appreciated that there is remarkably little intersubject variation under these experimental conditions The pattern of emptying shown in Fig 65 may be presented in another way by plotting the volume of the meal remaining in the stomach on a logarithmic scale against time on a linear scale with the result that the points fall on a straight line An example may be seen in Fig 66 which gives data for a patient with a duodenal ulcer This form of emptying may be described as exponential in that a fixed fraction of the volume of the meal leaves the stomach per minute the pattern of emptying shown in Fig 65 corresponds to an emptying of about 3 per cent of the volume of the meal remaining in the stomach per minute The time course of gastric emptying is thus similar in form to that of the decay of a radioactive material so that gastric emptying may also be described in terms of the half life of the process which is 22 minutes for the mean data of Fig 65

## THE GASTRODUODENAL PUMP

**Peristaltic rate**

Studies with radio opaque meals have established that the peristaltic waves sweep over the antrum but that when there is material in the antrum its systole does not expel the whole of its contents into the duodenum The usual rate of peristalsis is about 4 cycles per minute in man and an ordinary rate of gastric emptying is about 10 millilitres per minute assuming therefore that every systole expels some of the gastric contents the stroke volume is 2–3 millilitres The remainder of the antral contents must escape into the main body of the stomach through the advancing peristaltic ring as originally reported by Cannon (1911)

**Pressure gradients between the stomach and duodenum**

Quigley and Brody (1944) provided more details by studying in dogs the pressure gradients between the stomach and the duodenum simultaneously with the resultant movement of the gastric contents They reported that the movement of material began whilst the gradient was 3–4 centimetres of water and that there was a rise in antral pressure which preceded and outlasted that in the duodenal bulb the two cavities being separated by a closed pylorus during the period when their pressures were highest The closure of the pylorus began whilst the gastric contents were being discharged into the bulb thus accounting for the squirting action of the pylorus reported by early workers from their studies in dogs with duodenal fistulas (Carnot and Chassevant 1905) After the pylorus had divided the bulb from the antrum the pressures in both cavities reached 20–30 centimetres of water so that there was presumably some resistance to the onward passage of the contents of the bulb It may seem curious that movement of the gastric contents should depend upon gradients of a few centimetres of water whilst subsequently tenfold higher pressures were recorded However the pressure within a cavity is not a good index of the tension in its wall unless the radius is constant These high pressures were recorded when the lumina were minimal so that they may represent relatively low tensions in the walls of the antrum and duodenum

**Prevention of backflow**

It is interesting to note that in this outline of the cycle of the gastroduodenal pump the pylorus limits the duration of outflow from the antrum and would prevent backflow from the duodenum into the antrum were the pressure gradient favourable for this event It is therefore remarkable that Crider and Thomas (1937) found that wedging open the pylorus in dogs did not alter the gastric emptying time This observation does not indicate that the pylorus normally has no function but merely that when its function is prevented secondary regulating mechanisms cover up the deficiency As will be discussed later the composition and volume of the duodenal contents powerfully influence gastric peristalsis and emptying It must also be borne in mind that stimuli acting from within the stomach have been shown to influence the resistance of the intestine to filling (Gregory 1950) The role of the pylorus in restraining backward movement of duodenal contents is not its only activity for it may also limit onward progress from the stomach as may often be observed radiologically in man

TABLE

SCHEME FOR THE REGULATING MECHANISM OF GASTRIC EMPTYING

| *Stimulus* | *Receptors* | *Effects* |
|---|---|---|
| Acid in meal | Precardial | Slows emptying |
| Increase in volume of meal | Gastric | Hastens emptying |
| Acid in meal | Postpyloric | Slows emptying |
| Glucose potassium salts and fat in meal | Postpyloric | Slows emptying |
| Volume of gastric outflow | Postpyloric | Slows emptying |

## INFLUENCE OF THE VOLUME OF A TEST MEAL

A test meal must of necessity have volume and composition both of which have their influence on gastric function so that an understanding of gastric emptying must be based on studies of both these variables Because the possibility of variations of volume is less than that of variations of composition which range from plain water through the highest flights of good living the influence of volume on gastric emptying will be considered first

### Volume

It was shown by Van Liere et al (1937) that doubling the volume of a radio opaque meal lengthened but did not double the gastric emptying time The rate of gastric emptying must therefore have been increased but the radiological technique was not sufficiently precise to allow quantitative studies of the rate of emptying throughout the digestive period To obtain data on the influence of volume on gastric emptying serial test meal studies were made in 20 normal persons (Hunt and Macdonald 1954) Fig 67 shows data on the rate of emptying of the gastric contents after taking test meals of 330 750 and 1 250 millilitres of a solution containing 35 grammes of sucrose per litre The results are those for one subject who had a very rapidly emptying stomach The initial stage of emptying with the largest meal was accompanied by sweating of the face a sensation of coldness in the limbs and a rise of 20 millimetres of mercury in his diastolic arterial pressure The subject remarked that he normally sweated after meals This syndrome in a normal subject presumably corresponds to one type of post gastrectomy syndrome

Paying attention to the period 0–10 minutes it may be seen that as judged from the volume of the meal remaining the larger the meal the quicker the initial emptying After this first period however the smaller the original meal the quicker was the emptying The result is that with the largest meal the stomach gave a large priming charge to the intestine which then received material at an almost constant rate With the smallest meal the initial emptying was less but at a time when the emptying of the large meal had slowed the rate of outflow of the smallest meal reached a high rate Of necessity this rate declined rapidly The effect of this pattern of emptying is that with the largest volume a considerable proportion of the meal must enter the intestine after only minimal opportunity for intragastric digestion On the other hand a portion of the largest meal will remain in the stomach for a longer period than any of the material given as the smallest meal

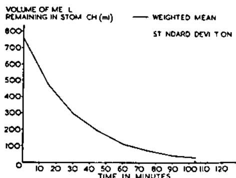



FIG 65 —Volume of meal remaining in stomach plotted against time (*By courtesy of the Editor of* J Physiol )

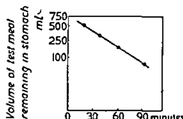



FIG 66 —The gastric emptying pattern for 750 millilitre test meal in a patieht with a duodenal ulcer

This particular pattern of emptying was first described by Marbaix in 1898 and has since been confirmed by Salamanca and Picazo (1943) and Hawkins et al (1953) The pattern is usually remarkably stable and robust It is relatively uninfluenced by some conditions which alter gastric secretion as is well shown by the data of Thornton et al (1955) who suppressed secretion by producing pantothenic acid deficiency in man leaving gastric emptying unchanged On the other hand in women there is a simultaneous change in gastric emptying and secretion in the middle of the menstrual cycle (Macdonald 1956)

There are two ways in which the stomach might be regulated to give emptying of an exponential form either the frequency of the strokes of the pump might become exponentially less or the stroke volume of the pump might become progressively less Radiological studies suggest that the frequency of the pump varies very little from 3 to 5 strokes per minute with the implication that the stroke volume of the pump becomes less as the volume of the gastric contents falls a relationship similar to that described by Starling s law of the heart lung preparation

## REGULATING MECHANISM OF GASTRIC EMPTYING

### Stimulation of extragastric receptors

The stomach is stimulated to empty by the volume of its contents but its emptying activity is governed by stimuli which operate on extragastric receptors proximal to the cardia and distal to the pylorus The term governed is used in a mechanical sense in that all the extragastric receptors which have been disclosed can be explained as inhibiting gastric emptying A list of the stimuli which operate the receptors influencing gastric activity is given in the Table The operation of the receptors distal to the pylorus is important in giving the reproducible pattern of emptying shown in Fig 65 for when test meals which exert a minimal action on the postpyloric receptors are fed the reproducibility of the results is greatly reduced (Hunt 1956) On the other hand the viscosity of the test meal which might be expected to influence the operation of the gastroduodenal pump directly had no detectable influence on gastric emptying (Hunt 1954) This finding allows unthickened fluid test meals to be used in most circumstances which is a considerable practical convenience

intestinal absorption of the initial priming charge plus the slow steady addition during the exponential phase of emptying is outpacing the rate of gastric emptying Since the stomach is usually empty at the beginning of meals (Roberts 1950) such a termination to an exponential emptying pattern was to be expected

Whether or not this type of emptying pattern is typical of the response to normal food is still open to doubt although there is some radiological evidence which suggests that the stomach treats normal meals in this way (McClure et al 1920 Wilson et al 1929) Moreover exponential emptying does not depend upon any special composition of the test meal since it occurs with various concentrations of sugar (Hunt and Spurrell 1951) and in the presence of bread (Salamanca and Picazo 1943)

From what has been written above it follows that the mechanism which regulates gastric emptying behaves as though it had a memory For example when the volume of the gastric contents is 250 millilitres the rate of emptying will depend upon whether this volume is the remnant of a 1 250 a 750- or a 330 millilitre meal Nor is it possible to dismiss this effect as simply the inhibitory action of the volume in the intestine acting to slow gastric emptying the enterogastric reflex of Thomas et al (1934) for it has been found that the second of two meals given in succession empties more quickly than the first (Hunt and Macdonald 1954)

## INFLUENCE OF SOME SOLUTES IN TEST MEALS

### Modification of osmotic pressure

It has been suggested that the stomach is a diluting reservoir which serves to modify the osmotic pressure of the gastric contents until it is iso osmotic with plasma In more recent work however (Shay and Gershon Cohen 1934 Van Liere and Sleeth 1940) the emphasis is placed on the regulation of gastric emptying by a duodenal mechanism which thus minimizes the osmotic stress placed on the delicate mucosa of the small intestine Moreover as test meals of high osmotic pressure do empty into the duodenum before there is opportunity of intragastric reduction of their concentration the effective diluting function of the stomach is minimal

When the osmotic pressure of a test meal is twice as high as that of the plasma the time of most rapid emptying is at the beginning of the digestive period before dilution can occur (Hunt and Macdonald 1951) Apperly (1926) pointed out that test meals containing 100 milliequivalents of sodium chloride per litre emptied very quickly Shay (1944) confirmed many of Apperly s findings by radiology and in particular showed that solutions introduced directly into the duodenum influenced gastric emptying Indeed the threshold of the duodenal receptors responding to composition appears to be lower than that of any similar gastric receptors which may exist (Keeton 1925 Luckardt et al 1919) so that the regulation of gastric emptying in response to change of composition of the gastric contents appears to depend mainly upon receptors distal to the pylorus (Marbaix 1898) Shay and Gershon Cohen (1934) were able to confirm that dilute solutions of sodium chloride and bicarbonate left the stomach more quickly than water but on the question of delay in emptying produced by sugars Shay (1944) writes for delay in emptying hypertonicity of the solution is a prerequisite However a repetition of experi ments similar to those of Shay using single withdrawals of the gastric contents

The emptying patterns for the three meals shown in Fig 67 do not at first sight appear to be susceptible to simple quantitative description but the relationship between these three patterns can be brought out more clearly by plotting the volumes of meal remaining in the stomach in the way shown in Fig 66 with volume on a logarithmic scale against time on a linear scale This has been done in Fig 68 which shows that for all three meals there was a part of the emptying pattern during which a straight line describes the relation between the volume of the meal in the stomach on a logarithmic scale and time For the meal of 750 millilitres this linear phase appeared to begin at zero time and to continue until the volume of meal was

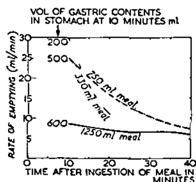



FIG 67 —The effect of the volume of meal ingested on the mean rate of emptying of the gastric contents (M B R M ) (*By courtesy of the Editor of* J Physiol )

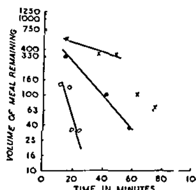



FIG 68 —The emptying pattern of the meal for subject M B R M initial volumes 1 250 750 and 330 millilitres (*By courtesy of the Editor of* J Physiol )

less than 40 millilitres after which the rate of emptying is known to be quicker than is demanded by the linear relationship (Hunt and Spurrell 1951) For the largest meal the initial rate of emptying was faster than is demanded by the linear relationship and there was also a terminal portion of 300 millilitres of the meal which left faster than is required by a continuation of the linear relationship

From a continuation of the line for the smallest meal towards zero time it appears that the rate of emptying only slowly worked up to the rate to be expected during the linear portion of the relationship between log volume of gastric contents and time A first fast phase of the emptying pattern was not detected with the smallest meal Looking at the sets of data for the three meals it may be seen that each has a linear phase and that the slope becomes steeper as the volume of the meal becomes less Expressed in another way the percentage of the meal emptying decreases as the original volume of the meal is increased and the effect of these two changes is that for the central part of the digestive period the rate of outflow from the stomach with large meals is actually less than it is with small meals as has already been shown in Fig 67 Consideration of this rather surprising finding however must include the fact that with the large meal the intestine receives a large priming charge The increase in the rate of emptying at the end of the digestive period has the result that material which has had an opportunity to be digested in the stomach is run into the intestine at a faster rate than is the same material during the exponential phase of gastric emptying Presumably this occurs at a time when

an alcohol with the same molecular weight as glucose and of potassium chloride all of which slow emptying as their concentration rises from zero A detailed discussion of these data is given elsewhere (Hunt 1956) They can be interpreted on the hypothesis that there is a single receptor mechanism in the duodenum and small intestine which is selectively sensitive to changes in effective osmotic pressure of the effluent from the stomach The common action of urea and sodium is of interest Since the majority of cells are penetrated by urea it is part of the working hypothesis that the receptor mechanism is permeable to both urea and sodium

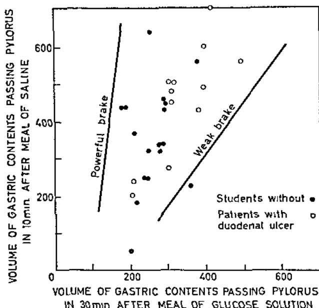



FIG 70 —The relation between the emptying of a test meal of glucose solution (100 g/l) and of saline solution (100 m equiv NaCl/l)

## ANALYSIS OF GASTRIC EMPTYING IN PATIENTS WITH DUODENAL ULCERS

The confirmation of the work of Apperly and Shay that solutions containing 100 milliequivalents of sodium chloride per litre left the stomach rapidly suggests a use for such test meals If these solutions leave the stomach more rapidly than any other their rate of emptying might be used as an index of the propulsive power of the stomach Thus by giving test meals of saline solution it should be possible to divide people into those with high and those with low gastric propulsive power The rate of emptying of a meal of a solution of glucose would then depend upon the interaction between the propulsive power and the opposing action of the duodenal braking mechanism operated by glucose Having an index of the propulsive power it should be possible to compare the power of the duodenal brake in different persons

after 30 minutes showed that even concentrations of sucrose giving a test meal of osmotic pressure half that of plasma slowed gastric emptying relative to test meals of distilled water with solutions of sucrose approximately iso osmotic with plasma the slowing of emptying was even greater (Hunt 1954)

These findings were clearly at variance with the hypothesis that the stomach may be conceived as acting as a reservoir protecting the small intestine from osmotic stress since by this concept meals hypo osmotic as well as hyperosmotic relative to plasma would be considered to provide stress These observations prompted a

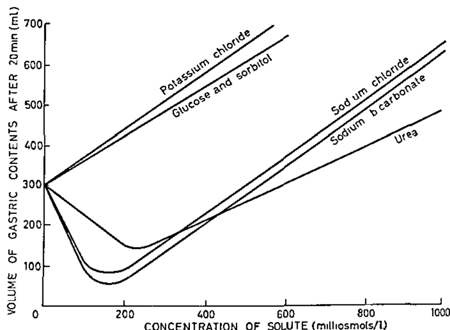



Fig 69 —The influence of the concentration of several solutes on the volume of the gastric contents 20 minutes after taking a 750 millilitre test meal *(By courtesy of the Editor of* J Physiol )

study of the influence of a variety of solutes on the emptying rate of test meals The results of a study on one subject confirmed by similar results in many others are shown in Fig 69 The subject was given test meals of 750 millilitres of solutions containing various concentrations of solutes and the gastric contents were withdrawn after 20 minutes In Fig 69 the volume of the recovered gastric contents has been plotted against the concentration of solutes expressed in milliosmols per litre of test meal This has the result that equal numerical values on the abscissa correspond approximately to equal osmotic pressures for different solutes It may be seen that the solutes fall into two classes As the concentration of sodium chloride sodium bicarbonate and urea rises from zero the volume of the gastric contents remaining at 20 minutes decreases to a minimum only to rise again as the concentration of these solutes increases above 250 milliosmols per litre In contrast to these results is the effect of increasing concentrations of glucose of sorbitol

an alcohol with the same molecular weight as glucose and of potassium chloride all of which slow emptying as their concentration rises from zero A detailed discussion of these data is given elsewhere (Hunt 1956) They can be interpreted on the hypothesis that there is a single receptor mechanism in the duodenum and small intestine which is selectively sensitive to changes in effective osmotic pressure of the effluent from the stomach The common action of urea and sodium is of interest Since the majority of cells are penetrated by urea it is part of the working hypothesis that the receptor mechanism is permeable to both urea and sodium

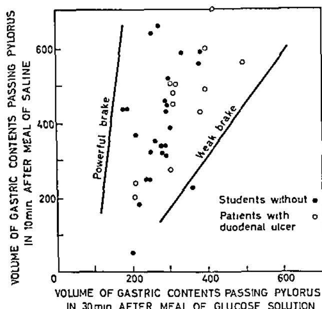



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The mean volume of the gastric contents with the saline-solution meal at 10 minutes was 427 millilitres (S E $\pm$ 20) in 47 male students without duodenal ulcer and 370 millilitres (S E $\pm$ 31) in 16 patients with duodenal ulcer the difference was not significant at the 1/10 level By this test therefore there is no difference in the propulsive power of the stomachs of a group of male patients with duodenal ulcer and a group of normal male students Furthermore normal men and women have equal propulsive powers

In Fig 70 the volume of the gastric contents passing through the pylorus with the saline solution meal in the first 10 minutes has been plotted against the volume of the gastric contents passing the pylorus with the meal of glucose solution in the first 30 minutes for 27 normal students and 16 patients with duodenal ulcer The data

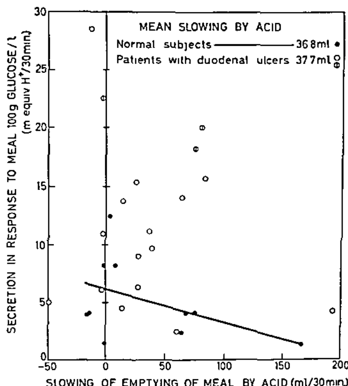



FIG 71 —Relation between slowing of emptying of meal in response to 20-m equiv HCl litre of test meal (glucose 100 g/l) and the amount of acid secreted in response to the meal in 30 minutes

*for both groups are so freely intermixed that there is no clear difference between* the effectiveness of the osmotic brakes in the two groups It should be noted that none of the patients with duodenal ulcers had any clinical evidence of pyloric stenosis

Occasionally it may happen that after partial gastrectomy patients complain of an uncomfortable sense of fullness and on radiological examination the meal of barium sulphate is seen to leave slowly In such circumstances there is the possibility that the gastric musculature may be weak that the inhibitory mechanism operating from the small intestine may be overactive or that the surgeon may have made the stoma too small One such patient given a *500 millilitre test meal* of saline solution (100 milliequivalents of sodium chloride per litre) emptied 400

millilitres of it in 20 minutes having previously complained that water produced a prolonged sense of distension After the test it was apparent that the stoma was adequate and the patient ceased to complain within a few days The result of this test suggests that where slow gastric emptying is undesirable—for example after gastrectomy or vagotomy—it might be advantageous to give the patient a saline solution containing 100 milliequivalents of sodium chloride per litre this is by no means unpalatable

Having failed to discover in patients with duodenal ulcer any defect in the duodenal receptors responding to glucose it was decided to investigate the influence of acid on gastric emptying Shay (1944) suggested that gastric emptying in anacid subjects was particularly susceptible to the slowing action of acid which is confirmed by the data for normal subjects as shown in Fig 71 The mean slowing of emptying of meal by the added acid was 37 millilitres in 30 minutes there was also a significant trend for the normal subjects who secreted least acid in response to the control meal to have their emptying most delayed by the added acid Shay further suggested that in patients with active duodenal ulcer acid was less effective in slowing emptying than it was in normal subjects The data shown in Fig 71 do not confirm this the mean slowing of emptying being 37 millilitres in normal subjects and 38 millilitres in patients with duodenal ulcer

As the patients with duodenal ulcer secreted on the average about twice as much acid as the normal subjects it would be expected from the relationship between secretion and the slowing of emptying by acid shown in Fig 71 for normal subjects that acid would be less effective in patients with duodenal ulcer than in normal subjects This in fact was not the case and it appears therefore that the mechanism by which the duodenum slows emptying in response to acid is if anything more effective in patients with duodenal ulcer than it is in normal subjects

It is remarkable that investigations with test meals which are sufficiently sensitive to show that a group of patients with duodenal ulcer secreted about twice as much as normal subjects have failed to give any convincing evidence that gastric emptying of saline solution meals or of meals of solutions of glucose or of acid is abnormally fast in patients with duodenal ulcers

## CONCLUSIONS

This account of some of the variables which influence gastric emptying may have some practical value in that it should establish that the stomach gives a reproducible response to a standard stimulus Thus a regime which is correctly founded may be expected to influence gastric function consistently The numerical values given may be of use in deciding the quantity and composition of the food which should be administered when the palate no longer serves as a guide

These points have their main significance in allowing clinicians to treat the stomach with the faith that gastric emptying is not capricious and that it can be controlled by simple measures

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# CHAPTER 11

# ANACIDITY

W I Card and W Sircus

## Historical introduction

The discovery of the secretion of hydrochloric acid by the stomach and the development of tests of gastric function made inevitable the detection of gastric juice in which no acid was present In 1894 Topfer s reagent (0 5 per cent dimethylaminobenzene in 95 per cent alcohol) was introduced and the term free acid was used to denote the acid titratable up to the change in colour of the reagent The term total acid was used to describe the titratable acid up to the change in colour of phenolphthalein The difference between these two points was described as combined acid The term achlorhydria* was used to describe the condition in which stomach juice failed to change Topfer s reagent though as is now known this change takes place at a $p$H of about 3 0–4 0 Achlorhydria and anacidity used interchangeably became current in various countries during the last decade of the last century The term achylia gastrica meaning an absence of any gastric secretion was apparently first used by Einhorn (1892)

In the last quarter of the nineteenth century the ionic theory of electrolyte solutions gained increasing acceptance and with it the concept of an acid in terms of the concentration of hydrogen ions The use of the notation $p$H the negative logarithm of the concentration followed in the first decade of the twentieth century Though the acidity of the gastric contents was first measured with an intragastric electrode by McClendon (1915) the definition of achlorhydria meaning absence of acid as detected by Topfer s reagent continued and is still extant at the present day This definition has produced the situation that after stimulation of gastric juice acid is said to be absent at a $p$H of 5 0 while at the same concentration of hydrogen ions another body fluid the urine is said to be strongly acid This kind of anomaly which depends on the arbitrary nature of any definition of achlorhydria was clearly recognized by Keefer and Bloomfield (1926) It has recently been discussed by Shay et al (1950) who concluded that since the $p$H of canine mucus was 8 2 achlorhydria could not be said to be present unless the gastric secretion was at all times about 8 2 or higher They naturally observed that true achlorhydria must be very rare indeed Any definition must clearly depend on the nature of the secretory stimulus the method of collection of the juice and the method of testing for the presence of acid The history of tests of gastric secretion has been marked by the use of increasingly powerful stimulants histamine insulin and latterly histamine in much larger doses coupled with an antihistamine drug (Kay 1953) by more certain methods of obtaining gastric secretion and by more refined methods of testing for the presence of acid This has resulted in an increasingly rigorous definition of achlorhydria

Throughout this chapter achlorhydria and anacidity are treated as synonymous and achylia as implying an absence of acid pepsin and intrinsic factor from the gastric secretion Achlorhydria will be defined later

In investigating achlorhydria it is necessary to consider critically the measurement of acid gastric secretion and the various factors this examination entails These factors include those which influence and dilute the primary acid secretion

Thro gh t th h pt rt d mm s sed d cal h t th t m ss sed d fined by th th q t d

the methods of stimulation the collection of juice and the methods of measuring acidity

## DILUTION BUFFERING AND DIFFUSION

A number of variable factors serves to reduce the acidity of the contents during tests of gastric function utilizing meals These include variation in the rate of secretion and of emptying dilution of the juice by the test meal dilution and buffering by swallowed saliva neutralization of the gastric secretion by regurgitated small intestinal secretions and variation in the secretion of acid buffers produced in the stomach and possibly in the rate of backward diffusion of H ions (Teorell 1933 1940)

The effect of variations in the rate of emptying and of secretion of the osmolarity and viscosity of the test meal and of the dilution by the meal material upon the recovered acidity of the gastric contents has been studied (Hunt et al 1951 Hunt 1953 Hunt and MacDonald 1954 Hunt 1954) These workers have shown that doubling the proportion of gastric contents leaving the stomach or doubling the rate of secretion has equal effects upon the result of the test meal (Hunt 1953) Thus no conclusion as to the secretory activity of the stomach can be drawn from a study of the changes of the acidity in the fractionally withdrawn gastric contents It is advisable to eliminate saliva by contamination and in practice this can be adequately achieved by instructing the subject to spit out accumulating saliva The use of a dental type continuous suction apparatus for aspirating saliva is found to stimulate salivary flow and to be uncomfortable for the patient

### Intestinal contents

The regurgitation of intestinal contents on the evidence of clinical and experimental observation does not appear to play an important part in altering the measured acid output from the secreting stomach Theoretically pancreatic secretion is capable of neutralizing an approximately equal volume of 0 1 N hydrochloric acid but gastric function tests on Mann Williamson dogs with the duodenal contents diverted to the ileum showed no change from the normal fractional gastric analysis curve (McCann 1929) and the acidity time curves of the secretory response to meals in the isolated fundic pouches of dogs show the same curves and deviations from maximal acidity as is found in fractional gastric tests in man (Ivy et al 1950)

After ligation of the common bile duct in experimental animals the acid output from the stomach was little altered (Hebert 1938) Likewise in a study in man in which bromosulphthalein was injected intravenously and its concentration measured in the aspirated gastric juice it was found that duodenal regurgitation played only a minor part in buffering the acid gastric secretion (Shay et al 1932)

### Non acid gastric secretions

The significance of the non acid gastric secretions and its relationship to the dilution and neutralization of acid is still *sub judice* The non acid component has been variously called buffering secretion alkaline constituent diluting secretion and non parietal component and is essentially made up of the mineral bases neutral chlorides bicarbonate mucin and pepsin

This secretion has been evaluated by a study of the quantitative relations between the secretion of acid and that of the various ingredients (Glass et al 1952) These authors demonstrated that the non parietal component is not a specific entity but a mixture of four complex secretions the pepsin together with some electrolytes secreted by the peptic cells mucoprotein neutral chloride and intrinsic factor from the fundal neck mucogenic cells the secretions of the gland in the antrum and cardiac region with mucus bicarbonate and possibly gastrin and the mucoproteins calcium salts bicarbonate phosphate and neutral chloride in the mucus from the surface columnar cells They deny the existence of the non parietal entity described by Fisher and Hunt (1950) but appear to have misunderstood the usage of the term by these authors They also observed that not more than 15 per cent of the hydrochloric acid is bound by buffers originating in mucin Since this is also true of pepsin which has insignificant acid binding power (Glass et al 1951) and since the buffering role of other organic substances derived from the stomach itself is insignificant owing to their small concentration (Komarov 1938) it appears that most of the organic buffers of hydrochloric acid are extra gastric and derived from salivary and a little from duodenal contamination The action of the inorganic buffers (bicarbonate and alkaline phosphate) is much more important Teorell (1933 1940) advanced the theory that variations in the acidity of gastric juice are in the main the consequence of simple diffusion processes hydrochloric acid secreted into the stomach continually losing H ions to the blood and gaining Na ions diffusing in the opposite direction the driving force being the concentration gradients through the dialyzing membrane represented by the gastric mucosa This exchange diffusion has been held to account for 50–80 per cent of the total acidity regulation (Elliot et al 1942)

**Incidence of achlorhydria**

Failure to recognize the fallacies in measuring gastric secretion which have been enumerated has resulted in widely varying estimates of the incidence of achlorhydria and its relationship to various disease conditions Thus Bennett and Ryle (1921) in their study of 100 healthy medical students established a complete absence of hydrochloric acid at all periods in 4 subjects They were using as indicator dimethylamino azo benzole and phenolphthalein (Topfer s) and as a result of this study it has been accepted that 4 per cent of normal subjects are constitutionally incapable of secreting acid Likewise our knowledge of the incidence of achlorhydria at various ages remains that provided by 3 studies made 25 years ago (Polland and Bloomfield 1930 Bockus et al 1932 Vanzant et al 1932) in all of which it seemed to rise from about 3 per cent (7 per cent in females) at 20–39 years to 25 per cent at over 60 years A critical re investigation of this incidence using modern methods is required

Enticknap and Merivale (1954) examined the results of 1 000 consecutive fractional test meals using the Bennett Ryle method and found an incidence of achlorhydria in 26 per cent of subjects over the age of 60 years and in disease states of various kinds it appeared in up to 50 per cent of the subjects As a result they concluded that achlorhydria is within the range of normal variation and its only value lies in excluding pernicious anaemia and in casting doubt on a diagnosis of duodenal ulcer

The necessity for re appraisal of the methods of testing gastric secretion and of the conclusions reached in previous studies was suggested by the following study

Fifty eight subjects consecutively reported to have achlorhydria after a test meal fortified by an injection of histamine base of 0 5 milligram were re examined screening the *aspirating tube into position stimulating solely by an injection of* 2 milligrams of histamine base and measuring the acidity of the aspirated juice both electrometrically and by titration In only 29 of the subjects was the failure to produce acid confirmed and of these 23 were cases of pernicious anaemia 5 of advanced iron deficiency anaemia with gross atrophic gastritis proven by gastro scopy and biopsy and 1 was a case of linitis plastica (Sircus 1956)

**Technical considerations**

*Stimulation*

Many stimuli for acid gastric secretion have been used in the past but histamine is the most potent and there is considerable evidence that it is in fact the actual substance responsible in the body for the stimulation of the parietal cell The effects of emotion (Bennett and Venables 1920) and of nausea (Grossman et al 1945) in suppressing gastric secretory responses are established A further advant age of histamine therefore lies in its relative independence from these interfering factors and also that contamination of the gastric secretions by food material is avoided In order to test for achlorhydria the maximum possible stimulus should be given and the augmented histamine test of Kay (1953) has proved satisfactory for this purpose

*Collection*

*To avoid losses through the pylorus or through the stoma when* gastric operations have previously been performed the withdrawal of gastric juice needs to be continuous As much as two thirds of stimulated gastric secretion may be lost through the pylorus if aspiration is practised only at intervals of 15 minutes (Kay 1953)

Repeated measurements of gastric secretion on subjects after gastroenterostomy and partial gastrectomy have been made (Marks 1956) A comparison of the results with and without prior blocking of the stoma with a dumb bell shaped balloon has shown that not more than 10 per cent of the measurable acid output is lost through the stoma or neutralized by jejunal regurgitation provided gastric aspiration is continuous An electric motor suction pump is satisfactory for continuous aspiration and the aspirating tube must be of adequate bore and with holes of reasonable size The Levine tube is superior to the Ryle s tube in these *respects*

**The maximal histamine test**

Not a single case of absolute achlorhydria was found in the first consecutive 500 subjects examined by the maximal histamine test (Card et al 1955) other than in subjects with pernicious anaemia The method used in this study and upon which our definition of achlorhydria is based is as follows

An aspirating tube of radio opaque material is passed in the subject and guided under the fluoroscope so that its tip lies in the antrum just beyond the right border of

the vertebrae The subject then assumes a position lying on the left side and fasting residue is aspirated from the stomach Continuous aspiration of basal gastric secretion is then begun and continued for one hour Forty minutes after beginning the continuous aspiration 100 milligrams of mepyramine maleate is given by intramuscular injection and at the end of the hour histamine acid phosphate 0 04 milligram per kilogram of body weight is injected subcutaneously Secretion is then collected continuously for a further hour All collections are titrated against $\frac{N}{10}$ caustic soda using Topfer s reagent as indicator and where free acid is not obtained the *p*H of the sample is measured by electrometry

If any bile contamination of specimens was present in a case demonstrating apparent achlorhydria the test was repeated with in addition duodenal intubation and aspiration

As a result of experience with the method of testing gastric secretion based on the maximal histamine response the authors suggest as a definition of achlorhydria that state of gastric secretion in which under the conditions of the test the *p*H of the secretion fails to fall below 6 0 following stimulation

## NORMAL SECRETORY MECHANISMS

Any consideration of the aetiology of achlorhydria necessitates some discussion of the normal secretory mechanism of the parietal cell A knowledge of this mechanism might be of therapeutic value since if achlorhydria can be induced in a patient with duodenal ulcer there is considerable evidence that the ulcer will heal

The nature of the mechanism that is responsible for the secretion of hydrochloric acid at a *p*H of less than 1 0 has always fascinated physiologists and biochemists It is now generally accepted that the source of hydrogen ions must be water and that therefore equal quantities of hydrogen and hydroxyl ions must be formed It has also been shown that for every molecule of hydrochloric acid secreted one molecule of carbon dioxide is necessary (Davies 1951) Though carbonic anhydrase plays an essential part in this process its precise role is undetermined

This secretory process requires energy which is ultimately obtained from glucose though the exact mechanisms of oxidation are not known Since this energy process is aerobic secretion must depend on blood flow and it has been calculated that something like 50 volumes of blood may be necessary to produce 1 volume of hydrochloric acid (Davies 1951) The maximal secretion of the stomach in man can produce the equivalent of 500 millilitres 0 16 N hydrochloric acid in one hour This implies the enormous blood flow of 25 litres per hour or over 400 millilitres per minute

In the living animal secretion of hydrochloric acid can be stimulated using the two main pathways of nervous and hormonal stimulation It has been suggested originally by Babkin (1944) that whatever the initial stimulus the ultimate sub stance responsible is histamine The evidence is considerable and has been recently summarized by Code (1956) who concluded dogmatically that histamine is in fact the local common chemostimulator of the parietal cells of the gastric mucosa If this is true the interest aroused by the use of histamine secretory studies in man gains immeasurably and the relationship that obtains between histamine stimula tion and secretory response assumes great importance

This relationship has been investigated in dogs by Obrink (1948) in dogs and in man by Hanson et al (1948) and in man by Adam et al (1954) The last named authors used continuous infusion of histamine over a three hour period and the resulting acid outputs lay on an S shaped curve Various theoretical explanations of this curve are possible but one of the simplest is to regard the output of hydro chloric acid as the result of a combination of secreting units in the parietal cell

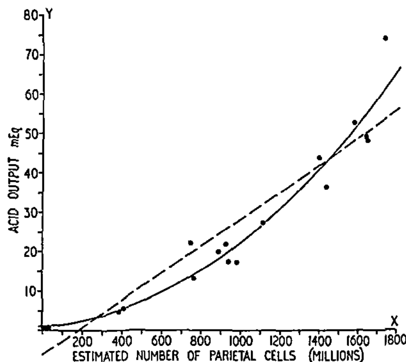



FIG 72 —Relationship of acid output to parietal cell population of stomach

with histamine molecules according to the laws of mass action The well known sigmoid logistic curve is the outcome and the results obtained fit this theory surprisingly well In terms of the theory the maximal response should be related to the number of parietal cells in the stomach or more precisely the secretory unit mass Various workers have shown a relation between acid secretion and the state of the gastric mucosa as revealed by gastric biopsy (Siurala and Lehtinen 1953) while Tongen (1950) showed a correlation between the maximal acidity of a previous test meal and the parietal cell count in the resected portion of the stomach

Though it is not yet possible to measure the parietal cell mass of the intact stomach it is possible to make parietal cell counts from the resected portion of a stomach after gastrectomy The maximal output of acid corresponding to these cells is estimated by measuring the acid output of the intact stomach and sub tracting the output obtained from the stump of stomach remaining after operation

By examining in this way a series of stomachs (Fig 72) it is possible to establish a strong correlation between the two variables parietal cell mass and the estimated acid output of the resected portion a correlation which is somewhat better if a power series is fitted (Card and Marks unpublished data) It appears therefore that under the conditions of this test outputs of acid are proportional to the numbers of parietal cells present and that low outputs are associated with few cells and since the curve runs through the origin no acid is associated with an absence of cells Though these conclusions are true of the material investigated they do not necessarily apply to all stomachs It does however seem probable that achlorhydria as encountered in clinical practice and defined as described above is simply due to an absence of secreting cells

## THE CLINICAL ASSOCIATIONS OF ACHLORHYDRIA

The gastric mucosa may fail to produce acid when hypothetical conditions as outlined in the Table are present all of which are associated with either structural or functional disturbance of the parietal cells

TABLE
HYPOTHETICAL AETIOLOGY OF REDUCED GASTRIC SECRETION

| | *Possible mechanism* | *Possible clinical associations* |
|---|---|---|
| Structural failure | | |
| Agenesis | Genetical failure of development of parietal cells | P A families |
| Abiotrophy | Early death of parietal cells | P A |
| Infiltration | Crowding out of parietal cells | Peptic ulcers |
| With simple cells | Interference with blood supply | Gastritides |
| With malignant cells | Action of toxic metabolites on parietal cells | Neoplasm |
| Degeneration | | Reticulosis |
| | Competition for metabolic substrates | Leukaemia |
| Functional failure | | |
| Anoxaemia of gastric mucosa | Ischaemia from shut down of vascular channels | Acute bleeding ulcer |
| Experimental metabolite deficiency | Hypochloraemia | Salt free diets |
| Enzyme deficiencies | Deficiency of iron vitamin B group | Sideropenic states<br>Avitaminosis |
| Endocrine | Deficiency of corticosteroids trophic hormones thyroxine | Addison s disease<br>Hypopituitarism<br>Myxoedema |

**Achlorhydria and pernicious anaemia**

The best recognized clinical association of true achlorhydria is with pernicious anaemia the cases seem to fall into three groups the commonest of which is the

familial abiotrophic groups in which some of the secretory cells of the gastric mucosa undergo early atrophy or disappear and the production of acid pepsin and intrinsic factor ceases The less common group is due to progressive inflammatory and degenerative changes in the mucosa with or without overt iron deficiency and proceeds ultimately to gastric atrophy Finally in the rare form there is a selective failure of production of intrinsic factor Mollen et al (1955) reported an interesting family the father of which had progressive gastric atrophy and pernicious anaemia over a period of 15 years he had diminishing gastric secretion until finally none could be obtained His son was found to have pernicious anaemia at the age of 13 months but at the age of 18 years despite studies with radio active vitamin $B_1$ confirming the diagnosis of pernicious anaemia had normal gastric mucosa and acid secretion Free acid is usually present in the infantile form of pernicious anaemia (Benjamin 1948 Reisner et al 1951) and there is some evidence that gastric atrophy may be a result of deficiency of vitamin $B_{12}$ Thus the output of acid from the stomach varied with relapse and remission in some cases (Murphy 1948 Mollen et al 1955) Vitamin $B_{12}$ like other vitamins in the B group may play a part in the enzyme system involved in the intermediary metabolism of cell repair and prolonged deficiency of it may result not only in degenerative glossopathy but also in progressive gastric atrophy Several papers have appeared on the association of free acid production with pernicious anaemia but not all of the older reports satisfy the modern rigorous criteria for the diagnosis of the anaemia (Beebe and Wintrobe 1933 Askey 1944 Murphy 1948)

By the time a clinical diagnosis of pernicious anaemia is made in all but the rare cases such as those quoted above the absence of acid pepsin and intrinsic factor is the rule (Weinberg 1951) The finding of anacidity however does not necessarily imply that intrinsic factor deficiency sufficient to give rise to clinical and laboratory evidence of pernicious anaemia will be present Weinberg (1951) quoted a personal series of 10 cases of achylia in which 7 developed pernicious anaemia in the next 6 years but Bloomfield and Polland (1933) followed 64 cases of anacidity for 5 years and none developed pernicious anaemia Where achylia is found in infancy this would seem to imply a generalized disturbance of gastric cellular development for of 12 cases of achylia followed from infancy up to the age of 14 years all developed pernicious anaemia (Miller 1941 1942) Wilkinson and Brockbank (1931) reported that 24 per cent of 291 relatives of patients with pernicious anaemia had achlorhydria regardless of age

That progressive structural change in the stomach may ultimately cause total failure of acid and pepsin production and of intrinsic factor is now well documented if not yet generally appreciated

**Progressive mucosal degeneration**

Badenoch et al (1955) reported the development of megaloblastic anaemia in 5 patients who underwent a partial gastrectomy for peptic ulcer within 2–17 (mean 8) years of the operation All showed free acid and normal gastric mucosa at the time of operation and all subsequently developed atrophy in the gastric remnant with a disappearance of secreting cells and a defective absorption of vitamin $B_1$ The authors have investigated a woman aged 60 years who had developed a megaloblastic anaemia 4 years after partial gastrectomy for a duodenal ulcer The remnant of the stomach showed almost total intestinal metaplasia and

no chief or parietal cells could be seen The appearance of the marrow and radio active vitamin $B_1$ absorption studies confirmed the presence of a true pernicious anaemia In our experience however an infiltration of the mucosa of the stomach with lymphocytes and plasma cells with varying degrees of loss of secretory ele ments in an associated atrophic process is a common observation in specimens resected in the treatment of long standing chronic duodenal and gastric ulceration and it may be that in a small proportion of such cases progressive changes continue in the remnant until full atrophy supervenes Markson and Davidson (1956) found well marked inflammatory atrophic gastritis in 2 and mild inflammatory changes in 4 out of 16 proven cases of pernicious anaemia examined by gastric biopsy

Complete failure of secretion of the different components of the gastric juice can undoubtedly occur though rarely Thus selective failure of intrinsic factor pro duction with a normal secretion of acid and pepsin from a mucosa rich in glandular tissue has been demonstrated in cases of pernicious anaemia (Mollen et al 1955) and selective total failure of production of acid and pepsin secretion in subjects with normal production of intrinsic factor (Doig and Girdwood 1957) The simultaneous investigation of the different components of gastric secretions in the same subjects would be profitable to further elucidation of the significance of failure of gastric secretion This has been attempted by MacLean (1955) assaying the renal excretion of oral vitamin $B_1$ $^{60}$Co He found evidence that combined intrinsic factor and acid deficiency appeared only in cases of pernicious anaemia or total gastrectomy as follows

| | *Percentage of vitamin B exc eted in urine* |
|---|---|
| 10 normal subjects | 6 7–31 |
| 5 subjects with gastric polyps | 10 –17 |
| 63 cases of achlorhydria based on triple injection of histamine | 5 –32 |
| 5 cases of pernicious anaemia | <1 |
| 10 subjects after total gastrectomy | <1 |

**Achlorhydria and iron deficiency**

The frequent association of chronic deficiency of iron with diminished gastric secretion deserves attention The possibility that this diminished gastric secretion was a result of chronic iron deficiency was envisaged by Davidson and Fullerton (1938) who pointed out that achlorhydria was increasingly common in females after the menopause whereas the incidence of anaemia was then declining Witts (1952) pointed out that the incidence of achlorhydria in a series of cases of uncomplicated iron deficiency anaemia rose with age The possible link between iron deficiency and gastric atrophy was suggested by Waldenstrom (1941 1942) who emphasized that iron was an integral part of Warburg s iron porphyrin and of the cytochromes a b c enzymes which were essential to the intermediary metabolism involved in cell multiplication and therefore in cell repair

Support for this suggestion that mucosal cell changes reflected the state of the iron supply was provided by Hallen (1938) who followed up 8 of Waldenstrom s cases of iron deficiency anaemia with achylia who were having treatment with iron From 3 to 15 months later 5 of the 8 were secreting hydrochloric acid and one of these on neglecting treatment had a recurrence of koilonychia and achylia

Three of the 5 cases had no free acid when the haemoglobin level was below 50 per cent but this appeared when the level of 80 per cent was reached However it is doubtful if satisfactory methods were used for testing gastric secretion

Important to the concept of the chronological priority of iron deficiency over achlorhydria is the observation of Heilmeyer and Plotner (1937) that absorption of iron may be normal in subjects with complete achlorhydria and of Schulten (1934) that cases of pernicious anaemia in remission rarely demonstrate evidence of iron deficiency

Unfortunately at present all reported investigations seeking to correlate the state of acid gastric secretion with that of the histology of the mucosa have suffered by not employing methods of stimulating gastric secretion which could be considered adequate in degree or quantitatively reproducible Most have accepted achlorhydria as the failure to obtain free acid after stimulation with doses of histamine of 0 3-0 5 milligram However some useful information has been provided by more recent studies

Badenoch et al (1957) have studied 50 cases of iron deficiency anaemia and attempted to correlate structure and function by taking suction b opsies of the gastric mucosa and measuring the acid response to 0 5 milligram of histamine and also the output of pepsin uropepsin and intrinsic factor They reported that achlorhydria was twice as common in cases of iron deficiency anaemia as in controls and four times as common if subjects under the age of 50 years were alone considered Only 1 of 7 subjects with iron deficiency anaemia but with normal or nearly normal gastric mucosa showed achlorhydria whereas it was present in 19 or 20 cases with severe glandular atrophy The secretion of pepsin and uropepsin correlated with the mucosal appearance in the same fashion and it is notable that in some of the cases in which glandular atrophy was found to be severe there was impaired absorption of vitamin $B_{1}$ which was improved by the oral administration of intrinsic factor with the vitamin They also noted that epithelial changes in the nails mouth and oesophagus were most commonly present in the group with glandular atrophy

**Achlorhydria and peptic ulceration**

The co existence of absolute achlorhydria with a peptic ulcer has been recorded on many occasions two quite recently (Sacks 1954 Howland 1955) despite the warning of Grossman (1951) that an apparent transient achlorhydria may occur in patients but if the diagnosis is correct (benign ulcer) they can almost always be made to secrete at least a small amount of acid with repeated testings Clearly much of this confusion arises from the definition of achlorhydria used We have had several cases of benign peptic lesions usually gastric but occasionally of long standing duodenal ulceration in whom the free acid response to histamine in doses of 0 04 milligram per kilogram of body weight was a slow as 0 5 milli equivalents in the hour after the injection and then demonstrated only after repeated testing—but we have not yet had a single case of benign ulcer in whom secretion of acid could not be demonstrated as occurring to some degree when measured by the electrometric technique and with repeated tests Such slight degrees of acid production implying the presence of some functioning parietal cells would not be detected by the methods used by any of the authors of previous reports on the association of benign ulcer with achlorhydria Furthermore Kahn (1937) and

Washburn and Rosendaal (1937) had 1 746 cases of pernicious anaemia between them without a single associated case of simple peptic ulcer

Palmer and Nutter (1940) following up 2 200 cases of peptic ulcer found none in whom achlorhydria persisted Some elucidation of the fluctuations in the secretory responses of subjects with peptic ulcer has been provided by the method of studying changes in the *p*H of gastric contents over the 24 hours used by James and Pickering (1949) and utilized in detail by Watkinson and James (1951) and Watkinson (1951 1956) The majority of gastric ulcer cases were observed by James and Pickering to show many hours especially at night when the output of acid was too low to be disclosed by titration methods or did not exist Watkinson and James studied 22 cases which failed to secrete free acid in response to histamine in 12 of whom a peptic ulcer was present and in 10 of these 12 cases a *p*H of 3 0 was exceeded for a mean of 9 8 hours of the day the lowest *p*H showed a mean of 2 1 Watkinson (1956) has recently analysed the results of a study of the *p*H over the 24 hours in 780 patients and the most interesting finding was that in 212 cases of bleeding peptic ulcer due to acute ulceration the majority demonstrated achlorhydria throughout the first 24 hours after bleeding commenced whereas this was never present when chronic duodenal ulcer was the cause and only present in the night hours in cases of chronic gastric ulcer The acute ulcer group remained achlorhydric for a mean period of 17 7 of the initial 24 hours Within a few days acid secretion reappeared in all but 1 case It is suggested by this study that a transient depression of parietal cell function is associated with bleeding Unfortunately the degree of neutralization produced by blood staining of many of the aspirated specimens was unknown

Thus it is demonstrable that where submaximal stimulation with histamine is employed cases of peptic ulcer with apparent achlorhydria will be found and where such cases are examined by repeated testing by the 24 hour *p*H sampling or by maximal stimulation with histamine acid secretion will be found in all The minimal level of *p*H (3 5) accepted by Watkinson as achlorhydria in the cases of acute bleeding ulcers is not in fact that of true achlorhydria but only that at which Topfer s reagent changes colour In these cases some acid must presumably have been secreted

It seems that only in the failure of functioning parietal cells which for practical purposes seem to be their structural absence is there found absolute achlorhydria

**Achlorhydria and infiltration of mucosa**

We have observed that all degrees of cellular infiltration of the gastric mucosa with a corresponding relative decrease in the number of functioning secretory tubules can be found in chronic peptic ulceration Around gastric ulcers a centrifugally distributed zonal gastritis often involves the parietal cell bearing area and could be responsible for affecting total acid output It has been shown (Hurst and Venables 1929 Watkinson 1951) that depressed gastric secretion may return to normal upon the healing of a gastric ulcer

Malignant disease of the stomach is usually associated with a lower than normal production of acid In our series examined by the maximal histamine test the average output for the post histamine hour is 7 2 milli equivalents (normal range 15–20 milli equivalents) It may be that achlorhydria will be found where the disease has extensively infiltrated the acid bearing area and particularly associated

with the scirrhous type of carcinoma or with infiltration by leukaemic sarcomatous and reticulosis cells

## Achlorhydria and avitaminosis

The association of achlorhydria and avitaminosis has been claimed in many studies but there is no modern work using refined techniques of examining gastric secretion and mucosa

The first reference to reduced acid output in pellagra seems to have been made by Angostoni (1893) From 50 to 70 per cent of various series of cases of avitaminosis and especially pellagra have been reported to have no acid response to histamine in doses 0 5–1 0 milligram (Mulholland and King 1931 Turner 1931 Guthrie 1932 Spies and Payne 1933 Spies and Chinn 1935 Spies et al 1939 Gillman 1944)

In an experimental study Williams et al (1939) induced thiamine deficiency in 4 subjects and observed over 21 weeks a gradual diminution or disappearance of free acid from the stomach but unfortunately no quantitative data are provided Mulholland and King (1931) followed up 31 patients with pellagra who showed no free hydrochloric acid after histamine stimulation and found that some recovered the ability to produce acid while others remained permanently achlorhydric despite clinical recovery from the pellagra It is noteworthy that these authors came to the conclusion that the clinical prognosis was generally worse in the cases showing achlorhydria

The damage appears to be incomplete however for it has been shown that gastric juice from pellagra patients without an acid response to histamine will nevertheless contain intrinsic factor capable of activating beef and bringing about remissions in pernicious anaemia cases (Spies and Payne 1933 Spies and Chinn 1935) The exact mechanism of these effects awaits suitable histological studies by modern technique but it seems likely that severe pellagra may damage the gastric mucosa beyond repair

### *Achlorhydria and mental states*

Various reports have appeared on the association of achlorhydria with psychosis (Henning and Norpoth 1932 a and b Wolf and Wolff 1948 Sackler et al 1955a and b) but none will stand up to critical analysis as the data provided are quite inadequate and the methods not precise Thus the last named authors based their findings in schizophrenia on single morning aspirations of gastric juice Nevertheless a careful study of gastric secretion in various psychotic states would be of interest

### Achlorhydria and endocrine disease

The status of gastric secretion in disorders of the endocrine glands likewise remains undetermined although numerous clinical publications claim an association of achlorhydria with myxoedema hypoparathyroidism and Addison s disease Data acquired by the authors on the response to the maximal histamine test in 7 cases of gross myxoedema showed a lower than normal output of acid in 4 cases 2 of which had coincident gastric ulcers and 3 being over the age of 70 years The output of acid was normal in 3 cases Treatment with thyroxine had no apparent effect on the response to the test The mucosal structure in a very severe myxoedema in a young male was essentially normal but showed heavy infiltration with plasma cells and only 2 8 milli-equivalents of acid was the response to the maximal histamine test No consistent changes in gastric secretion have been observed in Addison s disease using the maximal histamine test and none as the result of bilateral adrenalectomy with cortisone replacement in the treatment of carcinoma of the breast with metastases

A young female with gross hypopituitarism had absolute achlorhydria to the maximal histamine test and a young male with hypopituitarism showed no response to the large

dose of histamine the total output of acid in the hour after the stimulus being the same as that of the fasting control hour (4 0 milli-equivalents) In both cases daily cortisone administration over 3 weeks failed to alter the response in the maximal histamine test

In all of many cases of thyrotoxicosis examined by this test gastric secretion has been within normal limits

## INDUCTION OF ANACIDITY

Blocking nervous impulses by vagotomy the use of ganglionic paralysants or drugs which act on vagal nerve endings are procedures which inhibit secretion but do not except under special circumstances produce achlorhydria

If histamine is indeed the final common chemostimulator it might be possible by the use of a histamine antagonist to block the effect of all stimuli on the parietal cell The ordinary antihistamine drugs it has long been known have no inhibitory effect on histamine induced secretion why this is so is not clear A search has therefore been made for analogues of histamine which might have such an action but without success though the possibility of such a discovery still remains

There seems little doubt from a consideration of the energy mechanisms already discussed that any diminution of blood supply must limit the production of acid The surgical ligation of arteries has not proved very effective (Somervell 1948) Drugs that might diminish blood flow in the mucosa are noradrenaline and pituitrin and there is some evidence that inhibition of acid secretion can be obtained by their use (Cutting et al 1937 Harries 1956) Their action is however insufficiently potent to be of therapeutic value

Whatever the exact part played by carbonic anhydrase in the secretion of hydrochloric acid there is no doubt that this enzyme is an essential factor and its inhibition might therefore be expected to prevent secretion of acid Acetazoleamide a sulphonamide derivative has recently been synthesized and can be shown *in vitro* to inhibit secretion completely (Janowitz et al 1952) Though a significant effect can be demonstrated on the gastric secretion in man it is of little therapeutic importance (Janowitz et al 1955) Complete inhibition of carbonic anhydrase could not be tolerated in man The drug is therefore of little practical value for this particular purpose but its effect has great theoretical importance in that it acts on an enzyme system inside the parietal cell Inhibition of the enzyme systems involved in the intracellular energy mechanism should also inhibit secretion Oestrogens have been shown to inhibit secretion in animals (Ojha and Wood 1950) and to have a feeble though undoubted effect in man (Card unpublished data) it is possible that they act in this way

As Teorell pointed out many years ago secretion is accompanied by a diffusion of hydrogen ions back into the blood In his view this accounts for the different levels of acidity that are observed It might therefore be possible to induce achlor hydria by affecting the permeability of the mucosa to the passage of hydrogen ions so that a diminution of hydrogen ion concentration resulted There is some evidence to suggest that mersalyl introduced into the stomach has this property

Mention should be made of extracts of the intestinal mucosa and of urine which have been shown to inhibit gastric secretion These extracts have respectively been called enterogastrone and urogastrone but the names should not be

taken as implying that they contain a physiological principle their mode of action is unknown Though striking inhibitory effects have been claimed in experimental animals neither of these extracts has yet been obtained sufficiently pure to be used therapeutically

Achlorhydria can be produced by destroying the secreting parietal cell tissue by radiation from x rays or from radio active isotopes

Ricketts et al (1949) and Brown et al (1952) have treated a number of patients with duodenal ulcer by radiotherapy and have made simultaneous studies of acid secretion using subcutaneous histamine The total irradiation dose given was in the range of 700–2 500 roentgens The general effect of irradiation was to diminish secretion and the authors described the acute histological changes in the mucosa which followed to be replaced later by various combinations of atrophy prolifera tion metaplasia and fibrosis Achlorhydria defined as a failure to secrete free acid to Topfer s solution after subcutaneous injection of histamine 0 01 milligram per kilogram of body weight occurred more frequently in patients with gastric ulcer (68 per cent) than with duodenal ulcer (29 per cent) as might be expected The duration of achlorhydria was variable and rarely permanent though in some cases it continued for a number of years During the period of achlorhydria no ulcer ever recurred Even if complete achlorhydria is not achieved the effect of irradiation on stomachs which are capable of large secretions is certainly striking Attempts have also been made to achieve the same effect by using radio active isotopes in a flexible bag introduced into the stomach In experimental animals the technique has been successfully employed but it has not been used clinically (Douglas et al 1950)

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# CHAPTER 12

# PEPTIC ULCER

F Avery Jones and Norman C Tanner

## MEDICAL ASPECTS

Although peptic ulcer is a convenient term to cover both gastric and duodenal ulcers it must be appreciated that they may in fact be two separate diseases related anatomically rather than aetiologically This is strongly suggested by the varying behaviour statistically of gastric and duodenal ulcers which has been brought together in the Lumleian Lectures (Avery Jones 1957) It is particularly difficult to account for the striking difference in social class pattern and in hereditary behaviour except on the basis of their independence Duodenal ulcer is distributed evenly throughout the population but with gastric ulcer there is an excess among the labouring classes and a deficiency among the professional groups Both gastric and duodenal ulcers tend to run in families but those with gastric ulcers tend to have relatives with gastric ulcers and those with duodenal ulcers tend to have the same among their siblings and parents There have been two interesting developments in relation to the aetiology of ulcers recently first the correlation with blood groups and secondly the further studies on hypersecretion

### Blood groups and peptic ulcer

A most interesting recent discovery concerning peptic ulcer has been the correlation of the disease with blood groups The possible presence of appreciable differences in health in persons with different blood groups was first predicted by Fisher (1930) but the first convincing evidence of any such differences was the demonstration by Aird et al (1953) when they showed an increased susceptibility to gastric cancer of group A persons compared with O and B groups and this was followed by a similar survey for proved cases of peptic ulcer in which group A and group B persons were found to be less liable than group O These findings have been confirmed by Clarke et al (1955) and by many others The present evidence shows that duodenal ulcer is 1 4 times greater and gastric ulcer 1 2 times greater with group O than with the other groups

The blood group substances are mucopolysaccharides They are distinguished from each other by their antigenic properties There does not appear to be a specific antigenic blood group substance for blood group O but those who belong to group O have a mucopolysaccharide called H substance which appears to be present to a lesser extent in people who belong to other blood groups These mucopolysaccharides are present in small quantities in red corpuscles and in much greater amounts in body tissues and fluids and usually in the salivary and gastric secretions It is probably of considerable importance to find that not all persons are capable of secreting the ABO substances and preliminary results show that duodenal ulcer is 1 7 times more common among non secretors than among secretors (Clarke et al 1956)

There are two possibilities relating blood groups to peptic ulcer First the effect may be indirect or humoral and related perhaps to genetic control of gastric

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acidity and it may reflect a familial association Secondly it may be a direct association concerned with varying tissue resistance to an exogenous ulcerogenic or carcinogenic factor with blood group A protecting against ulcerogenic factors and blood group O protecting against carcinogenic agents Aird (1955) has suggested that a protective action like this may be more important than is suggested by the relatively small differences which are found between the different groups It might be for example that all the blood group mucopolysaccharides protect against both cancer of the stomach and peptic ulcer but that groups O and B protect more efficiently against cancer than A and that A and B protect more effectively against ulcer than O

**Hypersecretion of acid**

The mechanism of hypersecretion in duodenal ulcer has been elucidated by the studies of Kay (1953) and Hunt and Kay (1954) By increasing the dose of histamine stimulus to the stomach and neutralizing the systemic effects with an antihistamine it was demonstrated that the volume of the gastric response rose with increasing doses up to four times the normal body weight dose but thereafter more histamine produced no greater volume It is a reasonable assumption that at this dosage level the total secretory cell mass is operating and the volume of gastric juice represents the maximum secretory activity of the stomach With this test there is clear evidence of hypersecretion in a high proportion of duodenal ulcer subjects although there is appreciable overlap with the normal range as with other tests for gastric acidity They next demonstrated that with the same body weight dose of histamine the same percentage response was obtained in relation to the maximum secretory response in both normal and duodenal ulcer subjects Therefore there is no greater reactivity of the gastric mucosa in duodenal ulcer subjects as compared with normal persons This fits in with the hypothesis that there is a greater parietal cell mass in those with duodenal ulcer as compared with normals That this is so has been demonstrated by the elegant studies of Cox (1952) who from measurement of the stomach at necropsy demonstrated that those with duodenal ulcer have larger stomachs and more parietal cells than the general population This may link up with the sex incidence of duodenal ulcer Booth et al (1957) have shown that men secrete approximately 50 per cent more of acid chloride and pepsin than women but there is no difference in rate of emptying of the stomach

There may be two components to this greater secretory cell mass it may be hereditary and genetically controlled or it may be due to hyperplasia as the result of long continued nervous or dietetic over stimulation—or both factors may operate

**Medical treatment**

No striking advance in medical treatment has materialized in the past few years and it is doubtful if the many anticholinergic drugs are of any more value than atropine but it is likely that more potent depressors of acid secretion may yet be found

The evidence is regrettably slender that real benefit is derived from the traditional dietary regime and over treatment can undoubtedly be positively harmful There is fortunately a strong natural tendency to recovery for which the patient tends to give the credit to his treatment

Martin and Lewis (1949) reviewed a series of 365 patients with gastric or duo denal ulcers 10 years after in patient treatment and concluded It is undeniable that medical treatment relieves the discomfort of most relapses but from our present evidence we cannot believe that it is any protection against further trouble if this is destined by the ulcer Those cases which were active persevered with their regimen and also suffered complications while those who were inactive abandoned treatment and had no trouble Rae and Allison (1953) reached a similar conclusion from a follow up group of 63 men with proved peptic ulcer kept on a careful dietetic regime for 12 months and then reviewed after 5 years

Doll et al (1956a) compared an almost normal (fried free) diet with the standard ulcer regime in patients followed up for 1 year In their series there were 64 in patients with gastric ulcers 80 out patients with gastric ulcers and 50 out patients with duodenal ulcers The out patients were either advised to continue for 1 year on the standard ulcer diet with which they had previously been treated or were advised to revert to a wholly normal diet At the end of the year the proportion who had remained free from pain and in whom the ulcer was radiologically healed was practically the same in both groups

In studying the effect of alkalis and milk drip careful measurements concerning the rate of healing of gastric ulcer have been made with the addition of alkalis to a milk drip in sufficient quantity for the acidity of the gastric contents to be kept above *p*H 4 throughout the 24 hours This trial (Doll et al 1956b) demonstrated however that the milk drip produced a greater gain in weight—7 pounds (3 2 kilograms) compared with 3 pounds 8 ounces (1 6 kilograms)—and the impression was obtained that pain was relieved more rapidly with milk drip than without it and that it is therefore a useful adjunct to the standard treatment in patients whose pain persists after rest in bed Similar in patient therapeutic trials have been made with phenobarbitone ascorbic acid and bed rest (Doll and Pygott 1952) and with Robaden and cabbage juice (Doll and Pygott 1954) Two factors only have so far been demonstrated as having a beneficial influence (1) admission to hospital which implies bed rest and (2) cessation of the smoking habit

Even if there is no good statistical evidence for the beneficial effect of diet on the healing of ulcers it cannot be abandoned in the acute stage when the patient is undoubtedly more comfortable on a light diet

TABLE I

RESULTS OF TREATMENT ACCORDING TO SMOKING HABITS DURING TREATMENT IN PATIENTS WITH GASTRIC ULCER

| *Treatment (number of patients)* | *Percentage of patients in whom after 4 weeks ulcer niche was* | | | | | *Average amount healed (percentage)* |
|---|---|---|---|---|---|---|
| | *Healed* | *67–99 Healed* | *34–66 Healed* | *1–33 Healed* | *Larger* | |
| Advised to stop smoking and stopped (22) | 32 | 55 | 14 | 0 | 0 | 83 2 |
| Advised to stop smoking but failed to stop (18) | 22 | 39 | 28 | 11 | 0 | 71 8 |
| Not advised to stop smoking (40) | 25 | 33 | 18 | 15 | 10 | 56 6 |



FIG 75 — Zonal gastritis Gastric mucosa showing atrophic gastritis obtained under direct vision by the Benedict operating gastroscope from the site of anastomosis 7 years after a Polya subtotal gastrectomy for duodenal ulcer We have termed this gastro jejunal stomatitis The patient suffered pain and occasional vomiting Neither gastroscopy nor x ray examination revealed an ulcer Haematoxylin and eosin (× 130—reduced by one quarter in reproduction )

(1956) have recently discussed the problem of acid corrosive gastritis Alcohol may cause acute gastritis especially if consumed in high concentration and with diminished food intake

Using gastric biopsy Palmer (1951a) has demonstrated that when the damaging agent such as staphylococcal toxin has acted for only a short time the mucosa may undergo complete healing within 4 days However it may well be that persistent changes may occur if the damaging agent is severe or administered over a prolonged period X ray irradiation of the gastric mucosa provides an example of this prolonged effect (Ricketts et al 1948 Doig et al 1951)

*Aetiology of chronic gastritis*

In established cases of diffuse gastritis the aetiology of the mucosal change is obscure The average age of onset of symptoms of gastritis is 44 years this is similar to that in patients with chronic gastric ulcer (44 years) and contrasts with the earlier onset of symptoms of duodenal ulcer (average 36 years) (Doig and Wood 1952b)

Our experience is that chronic gastritis is more prevalent in the older age groups and long term studies suggest that the change is slowly progressive from superficial gastritis to atrophic gastritis and on rare occasions to almost complete gastric atrophy with subsidence of the inflammatory changes However it is wise to consider that neither gastritis nor gastric atrophy are normal in elderly people but have the same significance as in younger persons Palmer (1954c) found normal or nearly normal mucosa in 30 patients over 60 and without symptoms referable to the upper gastro intestinal tract

A family history of duodenal ulcer is common in patients with this condition (Doig and Wood 1952b) and to a lesser degree the same situation obtains with gastric ulcer (Doll and Kellock 1951) We were unable to find much reference to dyspepsia in the family history of patients with gastritis

In our experience chronic alcoholism is the commonest known cause of chronic gastritis this view was reported by Joske et al (1955) who found no apparent correlation between nutritional states and gastritis inferring that it is the direct effect of alcohol which is the cause of such gastritis These authors found that a survey of the dietetic habits and gastric biopsy findings of 695 subjects revealed

that with worsening of the nutritional status there was not a progressive deterioration in the histological structure of the gastric mucosa It is thus of interest that 51 of 95 chronic alcoholics had pronounced changes in the gastric mucosa on gastric biopsy These findings suggest that chronic alcoholism may be a cause of chronic gastritis but that malnutrition alone may not be a causal factor (*see* Table I)

TABLE I

CORRELATION OF GASTRITIS WITH NUTRITIONAL STATE AND ALCOHOLISM

(*After Joske et al* 1955)

| *Gastric biopsy findings* | *Nutritional state* | | | *Chronic alcoholism* | *Total* |
|---|---|---|---|---|---|
| | *Good* | *Fair* | *Poor* | | |
| Normal (including slight superficial gastritis) | 74 | 58 | 113 | 44 | 289 |
| Pronounced superficial gastritis | 62 | 65 | 121 | 39 | 287 |
| Atrophic gastritis | 48 | 29 | 86 | 11 | 174 |
| Gastric atrophy | 17 | 9 | 13 | 1 | 40 |
| Total | 201 | 161 | 333 | 95 | 790 |

Chronic gastritis is also common in certain chronic diseases such as gall stones (14 of 18 cases Joske et al 1955) and chronic pancreatitis (10 of 18 cases Mackay 1956) The implications regarding aetiology in such cases are unknown although the high incidence of chronic alcoholism in patients with gastritis and those with pancreatitis is of interest

At the present time it is impossible to speculate on the possible role of psychological factors in the aetiology of gastritis and the association which exists will be discussed with the symptoms of gastritis

*Chronic pyloric obstruction*

Ulcer or carcinoma causing obstruction may lead to generalized gastritis from gastric retention Biopsy studies in 33 patients with obstruction as a complication of benign ulcer revealed moderate or marked changes in the body of the stomach in 21 (Joske et al 1955)

*Pernicious anaemia*

Pernicious anaemia is associated with gross diffuse gastric atrophy and a corresponding depression of acid and pepsin secretion (Doig and Wood 1950) Usually the gastric biopsy reveals gross atrophy with marked intestinal metaplasia but in a minority there is a typical inflammatory reaction The simplest hypothesis is that this change is the end result of prolonged gastritis—the mucosa having passed through the stages of superficial gastritis atrophic gastritis and thence to gastric atrophy Several observations incline us to the view that this change is a primary non inflammatory atrophy patients with pernicious anaemia do not have a long history of indigestion The most unusual patient reported by Mollin et al (1955) had all the haematological features of pernicious anaemia but with normal mucosa and normal secretion of acid The patient reported by Robertson



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## THE CLINICAL FEATURES OF CHRONIC GASTRITIS

We still maintain the view expressed earlier (Doig and Wood 1952a) that in the absence of gross local disease of the stomach (or duodenum) upper abdominal symptoms and disturbances of eating in the pattern anorexia nausea vomiting are reasonably related to demonstrable gastric disorder both of structure and of function Joske et al (1955) observed that subjects with normal mucosa as shown by gastric biopsy rarely had clinical symptoms which could be attributed either entirely or partly to gastritis (frequency 1 in 16) whereas those whose gastric biopsy showed pronounced superficial gastritis atrophic gastritis or gastric atrophy had symptoms of gastritis much more frequently (frequency 1 in 3) (*see* Table II) We are unable to agree with Palmer (1954b) who related symptoms to a wide variety of lesions outside the stomach and duodenum It is also often suggested that since many patients with gastritis and achlorhydria have no symptoms gastritis and symptoms are not related Since gall stones may be found without colic dyspepsia or jaundice and peptic ulcer without symptoms such an objection merely points out our difficulties in understanding how symptoms arise in all three clinical conditions

TABLE II

**THE RELATIONSHIP BETWEEN GASTRO INTESTINAL SYMPTOMS AND GASTRIC BIOPSY FINDINGS**

(*After Joske et al* 1955)

| *Gastric biopsy findings* | *Gastro intestinal symptoms* | | | *No gastro intestinal symptoms* | *Total* |
|---|---|---|---|---|---|
| | *Indicative of gastritis alone* | *Indicative of gastritis in part* | *Not indicative of gastritis* | | |
| Normal (including slight superficial gastritis) | 12 | 9 | 225 | 99 | 345 |
| Pronounced superficial gastritis | 79 | 51 | 127 | 121 | 378 |
| Atrophic gastritis | 50 | 39 | 51 | 81 | 221 |
| Gastric atrophy | 11 | 5 | 5 | 35 | 56 |
| Total | 152 | 104 | 408 | 336 | 1 000 |

The average clinical picture of gastritis is of a middle aged patient with a history of indigestion for several years Symptoms intermit as in the case of peptic ulcer The chief complaint is of pain fullness or discomfort in the epigastrium occurring a short time after meals and seldom at night Despite the achlorhydria or hypo chlorhydria relief by alkali may occur but lacks the rapidity or completeness of the relief obtained by patients with ulcer With the recurrence of symptoms poor appetite nausea and vomiting may occur and injudicious selection or restriction of diet may lead to weight loss and vitamin deficiency Flatulence is common both in the presence of the above symptoms and in patients with gastritis but no other digestive complaints Apart from indigestion gastritis may occasion ally lead to haematemesis or melaena This description of the clinical picture of

et al (1955) had gastric atrophy 5 years before the onset of overt pernicious anaemia and subacute combined degeneration of the cord On the other hand we have observed 1 patient who usually has atrophic gastritis but occasionally shows a classical picture of gastric atrophy—that is a resolution of inflammatory changes in 7 years this patient has not developed signs of pernicious anaemia

## HISTOLOGICAL FEATURES

In this account we are most concerned with persisting gastritis of the acid secreting mucosa and have not considered gastritis of the antrum giant hypertrophic gastritis or acute forms of gastritis

It is useful to consider three stages of chronic gastritis In superficial gastritis the superficial epithelium of the ridges and pits shows varying degrees of irregularity the lamina propria shows an excess of cells which is maximal between the gastric pits and the tubules show minor changes some reduction in number and an increase in mucus secreting cells Atrophic gastritis shows similar changes in the superficial part of the mucosa There is a further progression in the loss of the gastric tubules and alteration of their epithelial lining and intestinal metaplasia with goblet cell formation is present in varying degree Gastric atrophy is the term we have used for the gastric lesion of pernicious anaemia the surface epithelium is tall and regular and intestinal metaplasia is more common the lamina propria is increased in amount but the wandering cell infiltration is minimal and the gastric glands are almost entirely absent being replaced by glands whose cells stain pink with mucicarmine or are lined by extensions of intestinal mucosa with frequent goblet cells These changes have been described by Magnus and Ungley (1938) they are unaffected by treatment (Doig and Wood 1950 Finckh and Wood 1953 Badenoch and Richards 1953 Siurala 1954 1956) (*see* Fig 76) The changes in gastritis have been described by Doig and Motteram (1950) Funder and Weiden (1952) and Motteram (1951) The changes following irradiation have been described by Doig et al (1951) Brown et al (1952) and Goldgraber et al (1954)



FIG 76 —Gastric atrophy with intestinal metaplasia in a patient with pernicious anaemia who had received full and successful treatment with whole liver extract and later vitamin $B_{12}$ for 13 years The biopsy fragment obtained by the flexible gastric biopsy tube extends down to the muscularis mucosae and shows no regeneration Haematoxylin and eosin (× 130—reduced by one quarter in reproduction )

*Effect of emotion on gastric activity*

The mechanism which underlies many gastric symptoms has been intensively studied in the fistulous subject Tom (Wolf and Wolff 1951) Most threatening situations for Tom led to an emotional conflict between a desire for aggressive and independent action and strong needs for support and approval and at the same time there was often gastric hyperfunction the motile stomach secreting more acid and the mucosa being engorged and more fragile Accompanying nausea there was relaxation and diminished secretion of the stomach and an increase in duodenal motility in amplitude and frequency with retrograde movements of duodenal contents (Wolf 1943 1949 Abbot et al 1952) With Tom in situations where defeat had occurred his reaction was of dejection and sadness and there was diminished gastric activity Similar findings were made in the other patients reported in the above studies The accompanying symptoms were those of fullness anorexia or nausea and occasionally vomiting that is similar to those described by us However no detailed study of the psychological state at the time of symp toms was made in our patients and the association of life stress and pathological changes in the stomach is at the moment speculative

## COURSE OF GASTRITIS

Fairley et al (1955) have made a study of the clinical course over 5 years of 32 patients with atrophic gastritis established by gastric biopsy at the beginning of the period Of 27 patients who had symptoms initially only 1 has shown remission while 4 have since had haematemeses In 3 the radiological examination showed some local lesion this was a small hiatus hernia in 1 benign gastric ulcer in 1 and a doubtful ulcer niche in 1 There were 3 examples of oesophageal regurgitation also seen on radiological examination while 22 other patients had no radiological abnormality Comparison of the results of histamine test meal in 25 patients showed that 8 patients had increased secretion of acid Although various factors may have been responsible for this change including decreased intake of alcohol (4) treatment of syphilis (1) and better diet (2) in none of these 8 cases was there gain in weight or decrease in symptoms None of the 32 patients showed any reduction in the inflammatory changes seen in the biopsy We feel that this con tinued history of symptoms is further evidence that gastritis can contribute to upper gastro intestinal symptoms Nine patients died from various causes—7 were examined post mortem and had no carcinoma of the stomach

## TREATMENT OF GASTRITIS

There is no specific treatment except the proscription of alcohol where indicated However armed with a positive diagnosis the physician can help the patient by reassurance about the absence of cancer encouragement to take a more liberal diet and sympathetic assistance in those of the patient s problems which seem related to his indigestion It is frequently reported that acid is of value in the treatment of gastritis or the patient with achlorhydria we have on occasion tried it but have not been impressed with the result The usual dose is quite inadequate to reduce the *p*H to a level which will promote peptic activity (Koehler and

chronic gastritis is confirmed by Rappaport (1955) in his description of patients with achlorhydria

Many patients who are subsequently found to have gastritis seek attention complaining of anaemia Changes in the mucosa were common in both hypo chromic anaemia of Witts and in the various macrocytic anaemias other than pernicious anaemia (Joske et al 1955) Davidson and Markson (1955) found gastritis in 31 of 42 patients with iron deficiency anaemia Since an appreciable number of such cases have normal mucosa it is clear that the achlorhydria or gastritis is not the chief causal factor Davidson and Markson suggest it is a consequence while the observations of Grace et al (1954) showed that iron absorption in one subject was independent of gastric acidity This suggests that in hypofunction of the duodenum in respect to iron absorption the same factors may lead to gastric hypofunction as well

*Clinical examination*

Physical examination is unrewarding Some 50 per cent of patients have diffuse epigastric tenderness and moderate to severe atrophy of the tongue is more common than would be expected in normal persons weight loss is of the same order as seen in peptic ulcer Again it may be said that gastroscopy and radiological examination have no direct role in the diagnosis of gastritis but serve to exclude local lesions of the stomach

When one compares the results of histamine test meal with the degree of histological change there is a direct correlation (Wood et al 1949b Funder and Weiden 1952 Joske et al 1955) with progression of the atrophy of the mucosa there is decrease in volume of gastric juice and output of acid and pepsin (*see* Fig 77) On these grounds it is probable that one can infer with some accuracy the

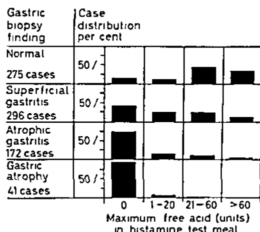



Fig 77 —Histogram showing relation between finding at gastric biopsy and histamine test meal (*after Joske et al* 1955)

likely histological findings at gastric biopsy from the results of a fractional test meal using histamine The capacity of the stomach to respond to an intravenous injection of insulin with increased motility is unaltered (Epstein 1949) Similarly the radiologist is unable to detect alteration in gastric emptying time as was originally suggested by Hurst (1946)

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Windsor 1943) Paradoxically many patients use alkaline powders but the pattern of relief does not resemble that achieved in peptic ulcer With these patients there is a slow decline in intensity which may continue over half an hour this is in contrast to the rapid response in patients with peptic ulcer (Bonney and Pickering 1946) Anaemia may be treated with ferrous sulphate or gluconate where iron is lacking Haematemesis or melaena should be managed along usual lines and rarely requires operation The diagnosis can seldom be made in the acute stage and we are distrustful of a diagnosis of gastritis made at laparotomy for bleeding when the stomach is not opened or when it is opened only after extensive handling from the outside

## GASTRITIS AND CANCER

The studies of Comfort et al (1947) have shown that achlorhydria and by inference gastritis are possible precursors of cancer and Ivy (1955) has suggested the importance of gastritis in this respect in a review of experimental work on gastric carcinogenesis So far we have no evidence to offer having regard to the 180 patient years in the study of Fairley et al (1955) whereas the incidence is of the order 1 per 1 000 in the over 60 years age group

## CONCLUSION

Gastric biopsy has afforded greater opportunities for the study of changes in the gastric mucosa in a wide variety of clinical situations and yielded much data about acute gastritis chronic gastritis and gastric atrophy In this review of our experience we feel we have established that chronic gastritis is a clinical condition the symptoms of which are played so to speak in a minor key From time to time the symptoms may assume greater proportions especially in response to psychological stress or over indulgence in alcohol while fear of cancer may be a factor in causing symptoms to be felt acutely and feared by the patient We are also confident that in a large majority of cases the distinction between severe atrophic gastritis and gastric atrophy has significance in relation to a diagnosis of pernicious anaemia and/or subacute combined degeneration of the cord Questions still unanswered include the aetiology of chronic gastritis or its histogenesis the precursors of the atrophy of pernicious anaemia and the relation of cancer and gastritis

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# CHAPTER 14

# STEATORRHOEA

W T Cooke and J M French

A general presentation of the steatorrhoea syndrome is given in the first series of this work in this volume therefore attention will be focused only on certain aspects of the condition

## DETECTION OF STEATORRHOEA

It should now be well recognized that the estimation of the percentage of fat in a specimen of dried faeces seldom provides reliable evidence as to the presence or otherwise of steatorrhoea The best that can be said is that where the percentage is more than 30 excess fat is likely to be present The introduction of improved quantitative measurements of faecal fat has been responsible for much of the increased awareness of the clinical significance of steatorrhoea To obtain these improvements balance data have been used Patients have been placed on diets containing a known amount of fat and the fat absorption (that is the difference between the amount of fat ingested and that excreted) calculated as a percentage of ingested fat However the percentage absorption in normal subjects tends to increase as the absolute amount of fat ingested increases although as Wollaeger et al (1947) pointed out the absolute amount of fat in the stools increases slightly also

*It has long been recognized that human subjects on a fat free diet excrete 1–3* grammes of fatty material daily (Sperry 1926) This is derived from non dietary sources such as epithelial debris residual material from secretions and synthesis by bacteria or other organisms while the possibility of actual excretion of fatty material into the intestinal lumen cannot be excluded

As non dietary elements of faecal fat cannot be satisfactorily assessed at present and percentage absorption varies with intake it is more logical to express results of faecal fat analyses simply as grammes excreted per 24 hours instead of relating this to intake and the expression percentage absorption should be abandoned Cooke et al (1953b) found the amount of fat in the stools of normal subjects on a 50–75 gramme fat diet to be 3 33 grammes (S E 0 19 gramme) Annegers et al (1948) added lard and hydrogenated vegetable oils to a basic diet to give a fat intake varying between 93 and 167 grammes of fat They found that the daily fat excretion for 40 subjects was 3 91 grammes (S D 1 56 grammes) Wollaeger et al (1947) found that the faecal losses of fat on a diet containing 101 grammes daily—the majority being cream and butter—were 4 1 grammes (S D 0 5 gramme) and on a 200 gramme fat diet 8 7 grammes (S D 0 7 gramme) They pointed out that according to observations published in the literature faecal fat showed a slight but definite increase with increase of the amount ingested

S E = Sta da d o    S D = Sta dard d to

The differences in fat excretion by normal subjects on mixed diets containing between 50 and 150 grammes of fat are small and almost within the limits of error of the various techniques for faecal fat estimation As ordinary mixed diets in the United Kingdom contain between 70 and 90 grammes of fat per day no significant errors in diagnosis should be made if the upper limit of normality for fat excretion is placed at 6 grammes daily From this it follows that an immense saving in time and effort can be made by dispensing with the use of carefully measured diets Stools should be collected over 3 or more days on ordinary diets and the fat content estimated daily or in bulk lots The rapid method of estimating the fatty acid content daily (Kamer et al 1949) is the most convenient and accurate enough for most purposes This generalization is applicable only to the detection of steatorrhoea as an aid in diagnosis

Exceptions to this practice must be made when patients are eating little and some care must be taken particularly with ill patients to ensure that adequate amounts of food are in fact eaten In subjects with malabsorption the intake of fat has a great effect upon the faecal output and any conclusions derived from study of the faecal fat output in such persons other than the fact that it is abnormal must be related to controlled intake In the case of patients excreting amounts on the borderline of normality the clinical history and the results of other tests must be taken into account before proper significance can be assigned to such figures If these exceptions are borne in mind the great bulk of faecal fat analyses can be carried out and logical conclusions drawn perfectly satisfactorily without diet kitchen facilities

**Nitrogen excretion**

Thaysen (1932) held that nitrogen absorption was little affected in idiopathic steatorrhoea and that the occasionally high values noted with diarrhoea in such cases were due to excretion from an irritated bowel It is still taught that nitrogen absorption is little affected (Bockus 1946) and this has often been regarded as a point in diagnosis from the steatorrhoea of pancreatic insufficiency in which it is well recognized that nitrogen absorption may be impaired

Recent work (Taylor et al 1952) has shown that the faecal losses of nitrogen in idiopathic steatorrhoea were sometimes quite as high as those in pancreatic insufficiency The absorptive defects for fat and nitrogen did not always appear to be of comparable magnitude Dreiling (1953) has made similar observations However in 6 cases Cooke et al (1953b) found a positive correlation between the fat and nitrogen and the amounts bore a striking resemblance to those found in 3 patients with non functioning pancreas or no pancreas at all It thus appears that where there is a large amount of fat in the stools there is likely to be an increased amount of nitrogen and that contrary to previous belief this latter finding has no significance in differential diagnosis between idiopathic steatorrhoea and pancreatitis How much of the excessive nitrogen excretion is derived from malabsorption and how much from other sources has not been determined There is however evidence that the nitrogen excretion in the steatorrhoea due to liver disease is not increased Gross et al (1950) found no significant increase of nitrogen in hepatitis and Laennec s cirrhosis in the presence of steatorrhoea whilst Atkinson et al (1956) found normal faecal nitrogen values in obstructive jaundice despite moderate to severe steatorrhoea

**Disturbances of electrolyte metabolism**

The normal subject passes 100–200 millilitres of water per day in the stools together with 2–5 milli equivalents of sodium and 10–15 milli equivalents of potassium Increase in the amount of water in the stools as for example in patients with diarrhoea is associated with an increase in the excretion of sodium in quantities which indicate a direct relationship between the two The amounts of sodium that may be found in severe diarrhoea can be as much as 200–250 milli equivalents per day

In patients suffering from non tropical sprue it has been found that there is an increased faecal excretion of potassium also In such instances the daily excretion of potassium is about 25 milli equivalents although on occasions as much as 60 milli equivalents may be found As the fluid content increases the amount of potassium remains relatively unchanged until large quantities of water are being passed (for example 1 000 millilitres in 24 hours) it then increases colnic contents remaining more or less isotonic with plasma The increase in potassium appears to be mainly endogenous in origin as the administration of large amounts of potassium by mouth under these circumstances does not lead to any significant further increase in the faeces it has also been found that 20 per cent of a dose of radio active potassium salt injected intravenously is excreted in the faeces Some faecal potassium may however be due to that present in unabsorbed food

The dangers of electrolyte depletion during severe diarrhoea is well recognized but the development of severe deficits following prolonged slight negative balance in patients with little or no diarrhoea as may be found in idiopathic steatorrhoea has not received the attention it deserves This aspect was studied by Blainey et al (1954) They showed by studies with $^{42}K$ in 12 patients with idiopathic steatorrhoea that the total exchangeable potassium for the males and females averaged 63 and 58 per cent of the mean normal values A further study of 23 patients with steatorrhoea the majority idiopathic by Flear et al (1957) showed similar results the average being 58 per cent of the mean normal values (range 15 6–82 per cent) A number of these patients had no diarrhoea

Wasting which is such a feature in idiopathic steatorrhoea is associated with considerable loss of muscle mass and the potassium findings can partly be explained on this basis but it was demonstrated in 16 of the 23 patients that the lowered total exchangeable potassium was due also to intracellular depletion In 20 of these patients the exchangeable sodium was estimated simultaneously with the potassium In none of these patients was there evidence of gross dehydration at the time of study and there was no evidence of significant deviation from the mean normal values

It has been pointed out by Moore et al (1954) that the serum levels of potassium are not a reliable guide to the state of the stores of exchangeable potassium The Birmingham United Hospitals figures confirm this observation in steatorrhoea as many of the 35 patients studied had normal serum values at times when their stores were low (Flear et al 1957a) It is important to realize therefore that in steatorrhoea many patients have deficient stores of potassium and that in some this is of severe degree

Potassium deficiency may play a part in the production of intestinal distension and ileus the peripheral neuropathy and mental disturbances weight loss and

renal tubular neuropathies occurring in the steatorrhoea syndrome Since pre vention is better than cure it is important to administer supplements of potassium salts whenever the patient is in relapse and from time to time when in good health

**Disturbances in water excretion**

Many patients with steatorrhoea show upsets in urinary excretion of water as evidenced by a marked nocturnal polyuria This symptom appears when patients are in relapse and usually clears up completely when the patients are well It can be a most troublesome symptom causing the patient to pass urine 4–5 times per night Even on a daily intake of 1 400 millilitres urine volumes as high as 4 milli litres per minute may be passed between midnight and one o clock whilst only small amounts are passed during the day an inversion of the normal rhythm in which small amounts are passed at night and larger amounts during the day

Wollaeger and Scribner (1951) drew attention to the poor diuresis that follows oral ingestion of water in patients with severe steatorrhoea and suggested that the nocturnal diuresis was related to the retention of large volumes of water in the intestines during the prolonged period necessary for the digestion and absorption of food They demonstrated clearly that the diuresis was not accounted for by renal disease or difference in posture during the night They also demonstrated that the time of maximal diuresis was influenced by the time of taking food and showed that increasing the fluid intake first increased the volume of the night urine When increased beyond a certain amount no further increase in nocturnal diuresis was effected and the daytime urine increased One point of clinical interest emerging from these observations was that some patients with steatorrhoea can give false positive results in the Kepler s water test for Addison s disease especially impor tant when it is remembered that many patients are pigmented (and a few may also have pigment in their mouths) have low blood pressures asthenia and often dis turbed serum electrolytes

By the use of heavy water Reitemeir et al (1956) have demonstrated that there is indeed a lower rate of absorption of water which corrects itself as the patient improves It is of interest that the rate was not speeded up by the administration of cortisone even though the patient s general condition approached normality with this therapy

Taylor (1954a and b 1955) extended the initial observations of Wollaeger and Scribner (1951) He agreed with their hypothesis of a delay in water absorption and pointed out the great delay in excreting water following the oral administration of one litre of water He found a significant positive correlation between the degree of this delay and the degree of impairment of fat absorption He did however find a similar delay in patients with untreated pernicious anaemia which almost dis appeared when treated though not returning completely to normal In pernicious anaemia Taylor believed that there was initially a delay in water absorption but a renal factor might also be implicated preventing the complete return to normal Observations in other conditions may provide a clue on the mechanism of the delayed diuresis in steatorrhoea

In a series of 28 patients with steatorrhoea Flear and Cooke (1957b) were unable to find any correlation between the degree of delayed diuresis and the defect in fat absorption nor could any correlation be found between the diuretic response and the serum proteins or degree of anaemia Little or no modification of the response

was noted with hydrocortisone The $^{24}$Na and $^{42}$K spaces were determined simultaneously in 9 patients No correlation could be found between the delayed diuresis and the exchangeable masses of sodium and potassium

Similar delays in diuresis were noted in patients with cirrhosis of the liver congestive cardiac failure ulcerative colitis and severe hypokalaemia whilst completely normal responses were obtained in 2 patients with severe hypoproteinuria The similarity in response in these several conditions raises the question as to whether the apparent delay in water and sodium absorption in steatorrhoea is the complete explanation of the upset in water excretion In 1 patient the nocturnal diuresis continued unchanged during the administration of fluid continuously for 7 days by a gastric drip without normal meals suggesting that there may well be some more fundamental defect causing this phenomenon This suggestion was supported by observations on patients with regional ileitis with steatorrhoea and apparently normal radiological patterns of the intestinal mucosa in the jejunum and upper half of the ileum In none was the faecal excretion of water more than 400 millilitres per day but in all there was the same delay in diuresis and increased nocturnal excretion of water Nocturnal diuresis in these conditions needs further investigation before the delay in absorption of fluid after meals as put forward by Wollaeger and Scribner (1951) can be accepted as the complete explanation

## TREATMENT

Diet has for long been the mainstay of treatment in the steatorrhoeas The various regimes in both adult steatorrhoea and even tropical sprue have been much influenced by the results in coeliac disease whilst those in the steatorrhoeas due to organic disease such as regional enteritis or post gastrectomy are often taken from those in use in the sprue syndrome although other treatments concerned with their specific pathologies have their place

## COELIAC DISEASE

Such great changes have taken place in the understanding of coeliac disease in the last few years beginning with publications of Dicke (1950) and Weijers and Kamer (1950) that some review of the dietary approach to treatment is necessary

From the time of the classical description by Gee (1888) it was considered that the intestine in coeliac disease was unable for some obscure reason to tolerate certain foods and efforts were directed to eliminate from the diet suspected undesirable substances Gee excluded fruits and vegetables and considered that cows milk was poorly tolerated though asses milk was beneficial he also observed that highly starched foods were bad for the patients with coeliac disease but that eggs and butter were satisfactory Schutz (1904) eliminated all fruits and vegetables Heubner (1909) recommended no fats or carbohydrates whilst Herter (1908) found proteins well borne fats moderately so and carbohydrates badly tolerated Writers continued to stress the fatty stools and the apparent difficulties with fat metabolism and it was natural that diets emphasized the reduction or elimination of fats Miller (1923) reduced the fats and increased the protein in the form of chicken eggs lean meat and fish and many other writers notably Parsons (1932) continued to recommend low fat diets

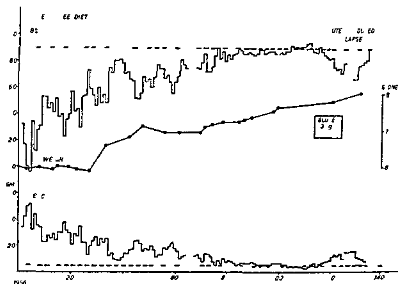
Howland (1921) recommended diets rich in protein based on the idea that carbohydrate must be rigorously excluded in the initial stages of treatment though there were frequent recurrences of symptoms as he later reintroduced carbohydrate into the diet Haas (1924) used a similar high protein diet to which he added bananas and other fruits and some vegetables after this a wider use of vegetables and fruits especially bananas may be noted in the literature Fanconi (1928) confirmed the value of fruits and vegetables and also reduced fat intake by the use of buttermilk or skimmed dried milk He observed that cane sugar and grain foods were not well tolerated Andersen (1947) excluded starches on the grounds of deficient pancreatic amylase

Certain general dietary rules had grown out of these many years of trial and error the main restrictions were little or no fat little or no starch little sugar and that as far as possible of a type least likely to undergo fermentation Starvation diets would undoubtedly have resulted had it not been accepted that a high protein intake was reasonably tolerated Even with careful dieting the disease ran a long drawn out course marked by many ups and downs and relapses lasting 2 or more years were commonplace Mortality was reported in different series to vary between 5–15 per cent and occasionally to be as high as 30 per cent

The great difficulty with the assessment of the value of the various diets was the fluctuating course of the disease itself with periods of improvement and deterioration for no apparent reason coupled with the lack of any acceptable criterion upon which to define day to day improvement Sheldon (1949) reported that the withdrawal of starch from the diet led to improvement in the fat absorption and Lowe and May (1951) made somewhat similar observations with complex carbohydrates

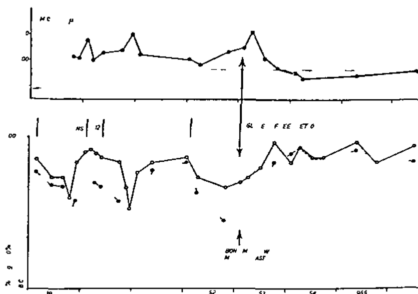
In the meantime it had been noticed by Dicke a paediatrician working in The Hague that children with coeliac disease who had been progressing very favourably under the conditions of starvation imposed by the war time German occupation of Holland began to fare less well with the reintroduction of adequate food immediately after its cessation He attributed this to the introduction of the cereals wheat and rye in the diet (Dicke 1950) and noticed that their withdrawal led to loss of symptoms the disappearance of diarrhoea and improvement of fat absorption These observations were extended by work in Utrecht (Weijers and Kamer 1950) and subsequent observations by these workers (Dicke et al 1953) showed that the offending portion of the wheat and rye flour lay not in the starch but in the protein fraction Their findings were quickly confirmed by others in Great Britain (Anderson et al 1952 Sheldon and Lawson 1952) and in the Scandinavian countries It seems clear from these studies that if wheat and rye flour is withdrawn completely from the diet the child suffering from coeliac disease becomes symptom free anaemia disappears appetite returns and growth is resumed at a normal or even increased rate for the child s weight and age Reintroduction of wheat or rye flour or the gluten or gliadin fraction of these cereals results in return to a state which is indistinguishable from the original illness and very small amounts (for example 1 gramme of wheat protein) daily may be sufficient Relapses of this nature may be initiated within a few days but clear up again rapidly with cessation of feeding the offending protein or whole flour

It is also clear that starch *per se* has no deleterious effect and a number of starchy foods have been specifically examined by the Dutch workers by feeding starch to




(*a*)

FIG 78 —(*a*) Influence of wheat free diet Fat excretion and absorption in a case of idiopathic steatorrhoea Female aged 50 years with 25 years history Gradual improvement over 110 days to normal Relapse induced with 30 grammes of gluten daily Symptom free for 4½ years No coeliac history The slow rate of improvement is noteworthy




(*b*)

(*b*) Red-cell changes in a case of idiopathic steatorrhoea on gluten free diet (same case as in Fig 78*a*) Improvements were obtained in the earlier years with liver extract cyanocobalamin and folic acid The mean cell volume however at no time during this period fell below the upper limits of normal After the institution of the gluten free diet rapid improvement took place without specific haematinic therapy and anaemia and macrocytosis disappeared

In considering the effect of the gluten free diet in tropical sprue it must be remembered that adult coeliac disease could develop for the first time in the tropics and might later well be regarded as chronic tropical sprue The chronicity of the illness and a favourable response subsequently to a gluten free diet should serve to differentiate the illness from true tropical sprue especially if relapse with gluten or flour containing gluten can be elicited It is well recognized that the tendency in tropical sprue is for the patients to be completely cured in a temperate climate on diets in which normal amounts of wheat are included

## THE GLUTEN MECHANISM

### Increase of faecal fat

Little is known of the precise mechanism by which wheat and rye glutens exert their effects upon the gastro intestinal tract and possibly elsewhere in the body It seems probable that if the illness has been established for some time the picture is much more complicated by malnutrition and avitaminosis due to defective absorption and other metabolic disturbances and in addition loss of electrolytes The study of the effect of gluten therefore simply by its withdrawal from the diet of ill patients might yield little information about the mechanism A more hopeful approach is that of allowing the patient to recover on a gluten free diet and then to study the influence on the metabolism of feeding gluten or its derivatives This has been done to a considerable extent by the Dutch workers whose studies clearly established that feeding gluten and gliadin led to an increased loss of fat in the faeces with increased looseness of the stool in most cases the observations with wheat gluten were confirmed in England (Anderson et al 1952)

The general view is that there is defective absorption in coeliac disease not only of fat but of all substances and this is supported by innumerable investigations The nature of the absorptive defect has been dealt with in the previous volume (Avery Jones 1952) Weijers and Kamer (1953) were of the opinion that there was an upset in the intermediary fat metabolism and that this fat was a true excretion The Dutch workers estimated the total saturated and unsaturated faecal fatty acid on a day to day basis and showed that in some cases the excreted saturated fat was in excess of the intake Subsequent studies with very low fat intakes showed a low faecal fat on a gluten free diet but when gluten was added the faecal fat increased in one case to 6–10 grammes daily although the intake was only about 1 gramme This amount was excreted for 2–3 weeks and the fatty acid was mostly palmitic acid

Streptomycin given to 1 patient did not alter the amount of fat excreted Al though similar findings have not been reported elsewhere fat excretion on a very low fat diet in patients with coeliac disease under such conditions has not yet been extensively studied The actual source of the excreted fat was not suggested by them but an increase in the rate of desquamation of intestinal cells seems a possible one

Excessive fat could come from other sources such as unabsorbed diet bile or intestinal secretions It could also be derived from intestinal organisms An interest ing finding of this nature has been made recently by Sammons et al (1956)

Cultures of a loopful of faeces from a case of sprue in 1 per cent glucose 2 per cent peptone broth showed visible and stainable fat on the surface of the medium within a few days The organism responsible appeared to belong to the *Streptococcus*

*faecalis* type (Lancefield group) The conversion ratio of medium to fat was high (250 milligrams of fat from 300 milligrams of substrate) In later studies they found that the addition of folic acid and sodium bicarbonate enhanced the fat production (Frazer and Sammons 1956a and b) In fact with the addition of 1 per cent bicarbonate and 0 6 per cent folic acid to the 1 per cent glucose and 2 per cent peptone the fat production was remarkable (500 milligrams from 460 milligrams of substrate total solids) A similar organism was cultured from stools of other patients with steatorrhoea and from a number of babies The demonstration of fat production by intestinal bacteria might prove a notable addition to knowledge and confirmation of these results is awaited with interest

**Denaturation of gluten**

Feeding denatured gluten and gliadin to children recovered from coeliac disease has been attempted Total hydrolysis of gluten and gliadin results in a soluble product consisting almost entirely of amino acids though some are destroyed in the process and there is a small insoluble residue The de acidified soluble material was harmless when fed to children with coeliac disease in amounts which would have caused relapse had the material been whole gliadin (Kamer and Weijers 1955) Weak acid hydrolysis results in de amidation and the more complete the de amidation the less was the toxicity The glutamine (glutamide) structure is con*verted to glutamic acid by this procedure and the results led Kamer and Weijers* to believe that the glutamine content was responsible for the toxicity However glutamine itself is non toxic in equivalent amounts None the less gliadin given by mouth to children with coeliac disease leads to a rise in glutamine blood levels above those in normal children though strangely glutamine itself does not Weijers and Kamer (1955) therefore believe that glutamine in bound form is dele terious It must be admitted however that glutamine occurs in other proteins for example casein in almost as high a concentration and yet even if given in large amounts it has no ill effect as it has in gluten or gliadin of wheat

**"Allergy**

It seems clear that it is the protein or some part of the protein of wheat and rye that is causing the reappearance of symptoms and signs in the child with coeliac disease A protein which is universally consumed in large quantities and which causes an abnormal reaction in a small proportion of the population raises the *possibility of an allergic basis for the unusual reaction though there is little evidence* for such a belief Allergic phenomena such as asthma hay fever or urticaria are not features of coeliac disease though occasionally asthma is encountered in adult idiopathic steatorrhoea Skin tests although frequently misleading in testing for tissue hypersensitivity have given no support to the idea (Collins et al 1954) Wheat and rye flour both of which cause deterioration in children with coeliac disease make dough suitable for breadmaking maize rice and buckwheat although containing gluten in comparable amounts can be fed in any quantity to children with coeliac disease without causing deterioration but do not make dough The dough making properties ultimately depend upon the chemical con stitution of the gluten This association therefore would seem to point to some peculiarity of chemical structure which is responsible for the effect in coeliac disease This is further emphasized by an antigenic relationship which has been demonstrated

between wheat and rye gluten (and also barley) by the induction of allergic and immunological phenomena in guinea pigs more significantly this cross relation ship does not extend to maize gluten (Wells and Osborne 1911 Lake et al 1914) An allergic reaction in a mucous membrane is characterized by hyperaemia and increased mucus secretion Although it is not possible to see the intestinal tract to determine if there is hyperaemia in coeliac disease and adult idiopathic steatorrhoea the small intestinal patterns visualized with barium sulphate pre parations indicate a gross excess of mucus secretion (Ardran et al 1950 Astley and French 1951) This appearance is not however confined to coeliac disease and adult idiopathic steatorrhoea It is seen also in tropical sprue and in a number of other conditions which are not allergic in nature It is possible therefore that the excessive mucus secretion in coeliac disease also is due to some cause other than an allergic reaction Gluten may contain some constituent which the child with coeliac disease is unable to metabolize like the normal person Fractionation of gluten has not clarified the issue as although chemical denaturation or *in vitro* digestion might destroy substances of a toxic nature these processes might equally well render harmless allergenic compounds There is at present insufficient evidence to show what is the mechanism of the gluten reaction in coeliac disease and adult idiopathic steatorrhoea

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# CHAPTER 15

# THE BLIND LOOP SYNDROME

JOHN BADENOCH

IT has been recognized for over 60 years that lesions of the small intestine can lead to severe malnutrition and to the development of anaemia

White (1890) seeking for the cause of pernicious anaemia described 6 patients in whom the small intestine was abnormal One of these was a man with a stricture 12 inches above the ileo caecal valve Faber (1895) reported a case with multiple strictures of the gut and suggested that the anaemia and failure to thrive might be due to the elaboration of toxins in the stagnant loops of bowel above the strictures As further cases were reported the evidence that intestinal disease could lead to macrocytic anaemia became stronger but the picture remained confused until the brilliant experiments of Castle and his colleagues set true pernicious anaemia apart from other conditions with a similar blood picture (Castle et al 1929) The early reports were largely concerned with the results of strictures of the intestine (Meulengracht 1929) but Little et al (1929) reported the occurrence of a macrocytic anaemia in a young man in whom an anastomosis was found between the jejunum and the ascending colon producing a blind loop of intestine

In the end it became clear that any intestinal lesion which produced stasis within the lumen of the gut either as a result of stricture or the formation of redundant loops of bowel could lead to the development of a syndrome characterized by loss of weight diarrhoea macrocytic anaemia and multiple vitamin deficiencies Gradually the condition came to be known as the blind loop syndrome and in recent years it has been the subject of three reviews in the literature

Barker and Hummel (1939) reviewed 49 cases and added 2 of their own Ten years later Cameron et al (1949a) reported a patient with a severe megaloblastic anaemia who was found at laparotomy to have a blind loop of ileum 70 centimetres in length (Fig 79) and they were able to collect a further 9 cases reported during the previous 10 years bringing the total number under review to 61 Of these 37 were suffering from strictures and 24 had anastomoses either entero enterostomies or entero colostomies Nine of those with anastomoses had either gastro colic or high jejuno colic fistulas Halstead et al (1956a) found 76 cases in the literature and reported 3 others which they studied in detail They pointed out that with the decline in incidence of intestinal tuberculosis and the improvements that have been brought about in surgical technique fewer cases of the syndrome have occurred in recent years

The earlier reports were concerned with the development of anaemia and malnutrition in patients with intestinal stricture or anastomoses but recently it has been shown that a similar picture may develop in the presence of extensive jejunal diverticulosis

Taylor (1930) reported a patient who had pernicious anaemia and a gastro enterostomy in whom autopsy revealed numerous diverticula in the jejunum Montuschi (1949) demonstrated a patient with diverticulosis of the small intestine

in whom the stools contained an abnormal amount of fat and Zingg (1950) drew attention to the fact that the sprue syndrome might result from diverticulosis of the intestine He described 2 patients 1 of whom had steatorrhoea and the other a megaloblastic anaemia but no diarrhoea but in this patient also the absorption of fat may have been abnormal Further cases were reported by Spang (1954) and by Krevans et al (1954) while Badenoch and Bedford (1954) described 2 patients with the triad of jejunal diverticulosis steatorrhoea and megaloblastic anaemia and suggested that stagnation within the narrow mouthed diverticula might

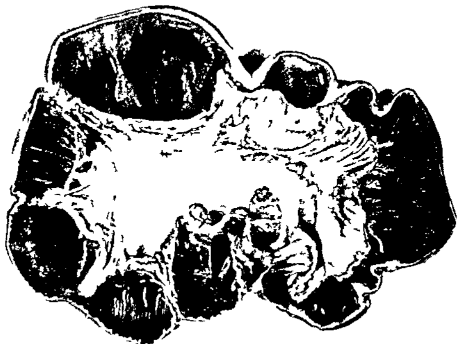


Fig 79 —Blind loop of ileum 70 centimetres in length bound together in the form of a rough circle containing 9 strictures with dilatations between them The free ends of the loop opened into the normal pathway of the bowel just above the ileo caecal valve (*Case of Cameron et al* 1949*a* )

produce an effect similar to a blind loop of gut In the first of these patients the condition was not recognized during life but at autopsy (Fig 80) massive diverticulosis of the upper part of the jejunum was found In the second radiological studies of the bowel revealed numerous diverticula containing fluid levels scattered throughout the small intestine (Fig 81) The condition does not seem to be very rare and other cases have since been reported (Paulley 1954 Dick 1955 Wilkinson 1955 Badenoch et al 1955 Halstead et al 1956 Blachford and Dawson 1956)

## PATHOGENESIS

Knowledge of the pathogenesis of the blind loop syndrome dates from Faber s prophetic statement in 1895 that the symptoms might be the result of elaboration

of toxins in stagnant loops of bowel Since then great advances have been made Today it is known that alterations in the flora of the gut and bacterial invasion of parts of the intestine normally sterile are the basic causes of the syndrome although the exact mechanisms involved are still far from clear

The importance of this bacterial invasion was first emphasized by Meulengracht (1921) who reported an autopsy on a patient with severe pernicious anaemia associated with tuberculous strictures of the ileum in whom the entire small

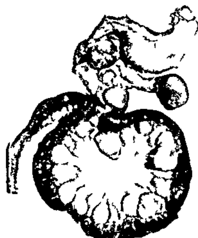


FIG 80 —Necropsy specimen showing the stomach pancreas duodenum and the proximal 4 feet of jejunum bearing numerous diverticula (*By courtesy of the Editor of* Quart J Med )



FIG 81 —Radiograph showing the massive duodenal diverticulum and numerous others containing fluid levels scattered throughout the small intestine (*By courtesy of the Editor of* Quart J Med )

intestine was loaded with bacteria The experiments of Seyderhelm et al (1924) lent support to the theory that bacterial invasion was important They induced fibrous strictures of the terminal ileum in 10 dogs Seven of the dogs survived the operation and 2 of these developed a fatal hyperchromic macrocytic anaemia In both it was found that gross bacterial invasion of the bowel above the strictures had occurred In the animals in which no anaemia developed the gut above the strictures remained sterile Similar experiments were carried out by Tonnis and Brusis (1931) who formed culs de sac in the small intestine in dogs In 15 animals *an anaemia usually hyperchromic in type* developed after 2–4 months It occurred more commonly when the cul de sac was formed in the jejunum than in the ileum and it could be relieved by excision of the sac by the administration of intestinal antiseptics or by liver extract

More recently Cameron et al (1949b) succeeded in producing a similar anaemia in rats by the formation of blind antiperistaltic loops in the small intestine The anaemia was macrocytic and haemolytic and was sometimes accompanied by steatorrhoea

Folic acid and chlortetracycline were effective in prolonging life and curing the anaemia but vitamin $B_1$ and liver extract were less so (Watson and Witts 1952) These experiments while providing strong evidence that lesions of the small intestine could lead to anaemia and malnutrition did not provide a complete explanation for the syndrome as it was seen in man Although the anaemia was often macrocytic and hyperchromic it proved impossible to demonstrate unequivocal megaloblastic change in the marrow of the experimental animals

However the link between the experimental anaemias in animals and the disease in man was close In the blind loop syndrome as it was seen in man neither loss of the ability to secrete intrinsic factor nor the presence of steatorrhoea could explain the anaemia in every case (Schlesinger 1933 Cameron et al 1949a) while the only factor common to all appeared to be the development of a lesion which produced stagnation and bacterial proliferation in some part of the gastro intestinal tract Restoration of the normal anatomy or sterilization of the gut by antibiotics would cure the anaemia and relieve the symptoms in man as in the experimental animals without recourse to any other form of treatment (Allen and Critchley 1951 Siurala and Kaipainen 1953)

Bacterial invasion of the upper bowel could explain most if not all of the manifestations of the blind loop syndrome Normally the upper intestine is sterile but once it is heavily contaminated gross disturbances of function may follow (Renshaw et al 1946)

There is evidence that many vitamins—among them biotin folic acid nicotinic acid riboflavine thiamine and vitamin K—are synthesized within the lumen of the intestine in man probably by bacteria (Welsch and Wright 1943 Najjar and Barrett 1945 Denko et al 1946) A change in the bacterial flora or the presence of abnormal organisms could therefore lead to vitamin deficiencies in the host by either the suppression of essential bacteria or the overgrowth of others which require the vitamins for their own metabolism The importance of intestinal synthesis in man at least of nicotinic acid and vitamin K has been emphasized by the occurrence of deficiency symptoms following the use of antibacterial agents (Ellinger and Mackenzie Shattock 1946 Heyeraas 1949) On the other hand bacterial competition is also important Vitamin $B_1$ although it does not appear to be synthesized in the small intestine in man (Dyke et al 1950) is an essential growth factor for many organisms including *Escherichia coli* (Burkholder 1952) Once the upper intestine has become infected bacterial action may lead to a consumption of the available supplies of the vitamin and a consequent deficiency in the host Other vitamins may be destroyed by the invading bacteria Vitamin C is not formed in the small intestine but it can be decomposed by bacteria from the gastro intestinal tract and in the presence of infection a high intake may be required to supply the needs of the body (Kendall and Chinn 1938 Young and James 1942)

Diarrhoea steatorrhoea and anaemia are prominent symptoms of the blind loop syndrome and any theory of its pathogenesis must explain their occurrence Here too abnormal bacterial action may be important Frazer (1949) has shown that organisms are present in the small intestine in patients with steatorrhoea and he has postulated that bacteria may ferment the starch and split the fat in the diet with the production of irritant fatty acids which are poorly absorbed and which give rise to diarrhoea and an outpouring of mucus This may be the cause of the

steatorrhoea but it may also be the direct result of bacterial action for Sammons et al (1956) have isolated an organism from the gastro intestinal tract which is capable of synthesizing fat in large quantities Once steatorrhoea has become established nutrition is further impaired and deficiencies of the fat soluble vitamins A D and K may be added to those already present

Anaemia when it occurs is usually macrocytic and megaloblastic and is the result of a deficiency of folic acid or vitamin $B_{12}$ or a combination of both The folic acid deficiency may be due to failure of intestinal synthesis to bacterial competition for the vitamin or in the presence of steatorrhoea to faulty absorption (Girdwood 1953) The deficiency of vitamin $B_{12}$ also depends on a number of factors The secretion of intrinsic factor may be impaired (Castle et al 1931) or the vitamin may be involved in the general failure of absorption that accompanies

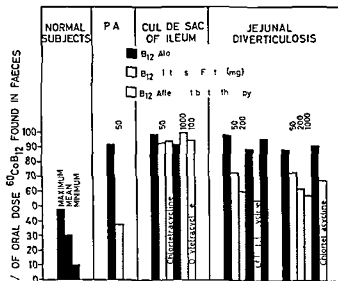



FIG 82—Effect of increasing amounts of intrinsic factor and of sterilization of the intestine with antibiotics on the absorption of an oral dose of 0 5 microgram of $^{60}Co$ labelled vitamin $B_{12}$ in 3 patients with megaloblastic anaemia and structural abnormalities of the small intestine

For comparison are shown the range and mean in 30 normal subjects given vitamin $B_{12}$ alone and the mean in 15 patients with pernicious anaemia given vitamin $B_{12}$ alone and vitamin $B_{12}$ plus 50 milligrams of the same preparation of intrinsic factor

steatorrhoea (Girdwood 1953) However the most likely explanation is that the bacteria present in the upper intestine compete for the vitamin and prevent its absorption The evidence for this stems from two main sources First sterilization of the gut by antibiotics can induce a remission of the anaemia (Naish and Capper 1953 Siurala and Kaipainen 1953 Friedlander and Gorvy 1955) Secondly the absorption of labelled vitamin $B_{12}$ can often be improved by the administration of antibiotics alone Fig 82 shows the effect of treatment with antibiotics in 2 patients with jejunal diverticulosis and 1 with a blind loop of intestine (Badenoch et al

## Gastric function

In contrast to patients with pernicious anaemia in whom histamine fast achlorhydria is the rule free acid is present in the gastric juice in 50 per cent of those with the blind loop syndrome (Barker and Hummel 1939) The results of other tests of gastric function are also variable The secretion of pepsin and the excretion of uropepsin may be either normal or greatly reduced (Badenoch et al 1955) Some of the patients retain the ability to secrete intrinsic factor but in a few this too may be impaired (Castle et al 1931 Schlesinger 1933 Verloop and Florijn 1951)

## DIAGNOSIS

Patients who develop the blind loop syndrome can be divided into two groups (1) those in whom there is a history of an abdominal operation in the past and (2) those in whom the condition arises spontaneously or as an incident in the course of a chronic disease of the bowel In the first group the development of a megaloblastic anaemia often combined with signs of iron deficiency or diarrhoea and loss of weight in a patient known to have had a laparotomy months or years previously should suggest the diagnosis Even if the cause of the symptoms is suspected it may be difficult to arrive at a definite diagnosis because the most careful radiological studies may not reveal the underlying abnormality

In the second group diagnosis may be even more difficult If diarrhoea is not a prominent symptom and the patient presents with a megaloblastic anaemia other causes for the condition have to be excluded In some the onset of symptoms at an early age the absence of a family history of anaemia and the demonstration of free acid and a normal secretion of pepsin in the gastric juice will exclude pernicious anaemia

In others who are elderly and who have histamine fast achlorhydria a reduced secretion of pepsin and a low serum vitamin $B_{12}$ the histology of the stomach from gastric biopsy may not show the gross atrophy of pernicious anaemia In difficult cases studies of the absorption of vitamin $B_{12}$ labelled with radio active cobalt may help to establish the diagnosis In pernicious anaemia characteristically the absorption of labelled vitamin $B_{12}$ is grossly impaired but is restored to normal by giving intrinsic factor together with the test dose (Callender et al 1954) In megaloblastic anaemia associated with the blind loop syndrome the absorption of vitamin $B_{12}$ is also impaired but little if any improvement can be obtained by the addition of intrinsic factor (Evans 1956)

As has been mentioned above in some patients signs of a coincident iron deficiency may point to an intestinal cause for the anaemia

## DIFFERENTIAL DIAGNOSIS

In those that present with diarrhoea and steatorrhoea a history of recurrent abdominal pain with episodes of subacute intestinal obstruction the presence of occult blood in the stools or radiological evidence of stricture or localized dilatation of the gut will distinguish the condition from idiopathic steatorrhoea When the syndrome is the result of jejunal diverticulosis it may be extremely difficult to exclude idiopathic steatorrhoea because the presence of the diverticula may

escape recognition The narrow mouthed sacs may not fill with barium and even if they do unless fluid levels are seen they may be mistaken for the flocculent clumps of opaque medium which are often present within the lumen of the intestine when the absorption of fat is abnormal On the other hand patients with jejunal diverticulosis usually develop symptoms later in life than those with idiopathic steatorrhoea and colicky peri umbilical pain is more common and difficult to relieve

## PROGNOSIS

Prognosis in the blind loop syndrome depends on the cause of the symptoms If they are the result of a simple stricture or some other abnormality which is amenable to surgery complete cure can be achieved If as is often the case there is widespread disease of the intestine the prognosis remains that of the underlying condition although it may be possible to cure the anaemia and to restore the patient to health at least for a time by medical measures alone

## TREATMENT

**Surgical intervention**

In the early days anaemia and malnutrition resulting from intestinal disease carried a very grave prognosis When Faber (1895) pointed out that stagnation of the intestinal contents might be the cause attempts were made to relieve the condition surgically The mortality rate was high because although the relief of the obstruction might be complete the patient s general condition could not be improved or the anaemia corrected before the operation nor could the sepsis which was almost always present be adequately controlled by the methods available at the time

Barker and Hunter (1900) stimulated by Faber s work attempted to relieve a jejunal stricture by performing an entero enterostomy but the patient died 2 days after the operation It was not until 1924 that Seyderhelm achieved the first successful surgical cure (Barker and Hummel 1939)

**Liver therapy**

Soon after liver therapy was introduced for the treatment of pernicious anaemia (Minot and Murphy 1926) it was shown to be effective also in megaloblastic anaemia resulting from intestinal disease Meulengracht (1929) reported the first success with liver by mouth in a patient who had been resistant to other forms of treatment and its effectiveness was soon confirmed by others (Castle et al 1931 Narbeshuber 1931) Further experience made it clear that although liver would correct the anaemia and improve the patient s general condition relapse occurred unless treatment was continued if the normal anatomy of the bowel could not be restored by surgery Unfortunately radical surgery is often impossible because the lesions are multifocal or the stagnant loops are part of a wider pathological process Haymond (1935) in a review of the literature on massive resection of the intestine pointed out that one third to one half of the normal small intestine could be removed without great impairment of function but when the bowel is diseased there is a much smaller margin of safety (Dvoskin et al 1952) In these cases surgery must be limited to the relief of obstruction and fistulas and treat

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supplies of iron should be given in the form of a non irritating oral preparation such as ferrous gluconate or by intramuscular or intravenous injection

In severe cases when the function of the bowel is grossly disorganized it may prove necessary to give all the vitamins and drugs with the exception of potassium by parenteral injection if a rapid remission is to be obtained

In the acute stage of the illness the use of a broad spectrum antibiotic (oxytetracycline 500 milligrams 6 hourly) may improve the general condition of the patient temporarily but the continued use of antibiotics can lead to the growth of a resistant flora within the lumen of the intestine and may have dangerous sequelae Finally in patients who fail to respond to other forms of treatment cortisone 300 milligrams or prednisone 60 milligrams daily may exert a dramatic effect Unfortunately here too if the underlying disease is progressive the improvement is likely to be only temporary Treatment with cortisone or its analogues requires very careful supervision for under their influence major intra abdominal catastrophes such as perforation of the gut or the formation of abscesses within the peritoneal cavity may be attended by remarkably few symptoms

Although in some patients the disease proves resistant to all forms of therapy the majority respond to treatment but even when a complete remission has been achieved it is necessary to continue treatment indefinitely if a relapse is to be avoided

## CONCLUSIONS

The blind loop syndrome is a rare condition but its importance lies in the fact that although it may occur in the course of chronic disease of the bowel not uncommonly it is the result of a surgical anastomosis All those who operate on the intestine should be aware of the danger of creating stagnant loops of bowel where bacteria may flourish and should limit such anastomoses below the stomach to cases where the immediate hazard to the patient or the grave prognosis of the underlying disease justifies the risks involved If as is often the case the creation of a blind loop of bowel is the only course open to the surgeon knowledge of the possible sequelae and the prompt institution of treatment should untoward symptoms arise will do much to avert a serious outcome

As the dangers of producing stagnant loops of intestine receive wider recognition it is probable that fewer cases of the blind loop syndrome will occur but in the past studies of these patients have shed light on the pathogenesis of the megaloblastic anaemias and have helped to increase our knowledge of the biosynthesis of vitamins in man

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*ment must depend upon supportive measures alone* Today many of these patients can be maintained in good health by medical treatment and it is often safer to treat them conservatively than to risk an attempt at a more radical cure Even when surgery is considered to be possible it is essential to improve the general condition of the patient by medical treatment before laparotomy is carried out

**Medical management**

A scheme for the medical treatment of patients with the blind loop syndrome is outlined in the Table It should include the provision of a high calorie high

TABLE

THE MEDICAL TREATMENT OF THE BLIND LOOP SYNDROME

*High calorie high protein low fat diet*
*(Supplement with high protein milk powder)*

| | |
|---|---|
| Whole B complex | Beplex 1 teaspoonful 3 times daily *or* Becosym 1 tablet 3 times daily by mouth |
| Folic acid | 20 milligrams daily by mouth |
| Vitamin $B_{12}$ | 100 micrograms monthly by intramuscular injection |
| Ascorbic acid | 50 milligrams daily by mouth |
| Vitamin A | 4 000 international units daily by mouth |
| Vitamin D | 10 000 international units daily by mouth |
| Vitamin K | (Water soluble analogue) 10–20 milligrams daily by mouth |
| Iron | Ferrous gluconate 5 grains 3 times daily by mouth |
| Calcium | Lactate or gluconate 15 grammes daily by mouth |
| Potassium | Chloride 2 grammes daily by mouth |

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protein low fat diet with full vitamin and mineral supplements Many cannot tolerate large meals and the addition of a high protein milk powder such as Casilan 4 ounces daily will provide useful calories and protein without much increase in bulk Multiple vitamin deficiencies are common and this syndrome provides one of the few rational indications for shot gun therapy Whole B complex ascorbic acid and vitamins A D and K the latter in a water soluble form may all be required In the presence of steatorrhoea in addition to the fat soluble vitamins supplements of calcium iron and potassium must be given Calcium to be effective must be used in much larger doses than are commonly required—up to 20 grammes of calcium lactate or gluconate daily The large doses of calcium salts not only meet the need for calcium but exert a beneficial effect in controlling the action of the bowels if diarrhoea is troublesome In steatorrhoea also the bulky stools may contain large quantities of potassium and it is necessary to give additional potassium chloride or citrate to make up the loss

Adequate treatment for the anaemia plays an important part in management In recent years there has been a tendency to regard the intestinal megaloblastic anaemias as being due primarily to a deficiency of folic acid rather than to lack of vitamin $B_{12}$ It is true that an excellent haematological remission may be obtained with folic acid but treatment with this vitamin alone is hazardous Recent work indicates that these patients also suffer from a deficiency of vitamin $B_{12}$ (Evans 1956) which may lead to the development of subacute combined degeneration of the cord if folic acid only is used Iron deficiency is common and additional

supplies of iron should be given in the form of a non irritating oral preparation such as ferrous gluconate or by intramuscular or intravenous injection

In severe cases when the function of the bowel is grossly disorganized it may prove necessary to give all the vitamins and drugs with the exception of potassium by parenteral injection if a rapid remission is to be obtained

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## CONCLUSIONS

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# CHAPTER 16

# MASSIVE RESECTION OF THE SMALL INTESTINE

W P U JACKSON

THIS chapter is concerned almost solely with large resections of small bowel because there are no after effects related directly to loss of smaller lengths Haymond (1935) pointed out that 200 centimetres represents about one third of the length of the small intestine and was according to the experiments of Senn (1887) the maximum amount of small bowel which could be removed with safety from an adult patient Hence removal of more than 200 centimetres was termed extensive or massive Since 1935 however it has become evident that much larger amounts may be removed—at least from the metabolic standpoint It would now seem more reasonable to consider as massive the resection of at least two thirds of the small bowel (over 400 centimetres) If this is conceded then only 38 of Haymond s 257 collected cases would qualify for consideration and in only 4 of these was more than 600 centimetres removed

The clinical metabolic and anatomic effects of really massive resections are important from the viewpoint of the surgeon who with improving supportive and anaesthetic techniques is increasingly tempted to remove large tracts of gangrenous gut Furthermore study of such cases is teaching us a good deal of applied physiology of the small intestine

## LENGTH OF THE SMALL INTESTINE

It has been suggested that 400 centimetres of small gut is an important figure but actually the length of the organ is so variable that the only valid criterion with regard to a patient s prognosis or future disability is the amount left behind There have been very many reports concerning the normal length of the small gut but unfortunately the considerable lengthening which takes place after removal or after the patient s death has not always been appreciated Thus Haymond added together the findings at operation and autopsy of some 15 authors to make an average of 21 feet 6 inches (657 centimetres) for 1 161 adults with a range of 10 feet (304 centimetres Bryant 1924) to 40 feet (1 216 centimetres Lamb 1924) More recent measurements by Cleland (1944) and Underhill (1955) are essentially similar Hirsch et al however measured the small intestine during normal life by an intubation technique in 10 adults and found a mean length of only 261 centimetres Raeburn and Brafield (1956) report two patients with small bowel lengths of only 4½ feet and 6 feet both of whom died from hepatic cirrhosis

## REASONS FOR RESECTION

In Haymond s collection the commonest cause for resection of over 200 centimetres was volvulus including a particular variety known as *Knotenbildung* and described in patients who lived in the Baltic regions In this type a knot is found which involves ileum and sigmoid flexure (Faltin 1906) Other common causes were strangulated hernia mesenteric thrombosis disease of the female

pelvic region (especially uterine perforation) tumour and other disorders of the mesentery abdominal injuries intestinal tuberculosis adhesions and bands

Perforation of the uterus with a curette especially at the time of criminal abortion damaged the mesentery and allowed prolapse of extensive lengths of the small gut Three of the four cases in Haymond s survey in which more than 600 centimetres were resected belonged to this group In none of the recent reports has this particular insult been described as the reason for resection In three other cases the small intestine prolapsed through a slit *in the mesentery and became* incarcerated Volvulus was found to be the worst risk from the point of view of immediate mortality being 52 6 per cent in Haymond s series

The commonest causes of really massive resection in recent years have been mesenteric vascular occlusion and volvulus In a number of patients regional ileitis has necessitated the operation a condition which probably masqueraded as *tuberculosis at the time of Haymond s review thus accounting for the* surprisingly good results with only 2 deaths in 16 cases of resection for tuberculosis Lymphoma sarcoma and polyposis of the small intestine are further causes

## HISTORICAL LANDMARKS

Haymond (1935) believed that Koeberle in 1880 was the first to have a patient survive following resection of over 200 centimetres of small intestine Senn (1887) was probably the first to report systematic studies of the effects of experimental removal of lengths of small intestine in animals

Three early resections of over 500 centimetres together with some follow up data were described by Vitali (1903) Denk (1907 1911) and Axhausen (1909) Several other *early cases collections from the literature and results of resections in animals were* reported but the publication of Flint (1912) was outstanding and combined a review of 56 cases with his own experiences and with the results of his experimental work on dogs In the latter he observed a variability in response in that while some dogs might live quite normally after removal of 80 per cent of small gut others would never really recover after only 60 per cent had been excised and would easily fall prey to any intercurrent upset He found a profuse diarrhoea and marked loss of weight immediately after the operation followed by a slow recovery until the animal might pass one stool a day and even become constipated At this stage the fat and nitrogen lost in the stool might be as high as 75 per cent of the intake but a normal fat absorption could be produced by reducing the amount in the diet Carbohydrates were perfectly normally absorbed even if the intake were increased fourfold

Matthaei (1925) reported on a patient who lived in good health for 11 years following *resection of 530 centimetres Haymond s review (referred to above) surveys the litera*ture up to 1935 Subsequently there have been very many individual cases reported in which less and less small bowel has been left behind The limit has been reached by Martin et al (1953) who removed the entire jejunum and ileum following superior mesenteric arterial obstruction The third part of the duodenum was anastomosed to the transverse colon and the patient a man aged 46 years lived for 316 days The most detailed metabolic investigations following resection have been made by West et al (1938) Todd et al (1940) Althausen et al (1949 1950) Jackson and Linder (1951a and b 1953 1955) and Linder et al (1953) The last named authors were able to follow one patient* closely for 3½ years after the loss of all but 7 inches of the jejunum and ileum and to correlate the results of their study with autopsy findings

* Th p t nt will be m nt d f eq tly beca se se l in i g t o pe fo m d o him appe r t h e o c nt rp ts n th l t rat e H w ll be ref ed t s To

Several more recent workers have extirpated lengths of small intestine from experimental animals usually dogs but the most outstanding reports have come from Denmark (Petri et al 1942 Jensenius 1945)

## EXTENT OF RESECTION

The early experimenters seemed largely interested in the problem of how much of the small intestine may reasonably be resected Despite Senn s condemnation of removal of more than one third it soon became evident that variable amounts from 50 to 85 per cent could be resected from dogs with complete recovery and a healthy life thereafter (Monari 1896 Erlanger and Hewlett 1901 Evans and Brenizer 1907 Flint 1912 Wildegans 1925 Kunz and Molitor 1928 and Jensenius 1945)

In man the variability seems greater On the one hand there are reports of resection leaving as little as 18 inches of small intestine followed by excellent health (Meyer 1946 Berman et al 1947 Cogswell 1948) while the patient reported by Croot (1952) for example was well 10 years after removal of all but 4–5 feet of small gut Jerauld s patient is reported well after 22 years (Weckesser et al 1949) A man aged 70 years (Cattell 1945) had no ill effects from loss of 86 per cent of the small bowel On the other hand removal of 200 centimetres or even less has in other cases been followed by a downhill course Thus the second patient of Posey and Bargen (1948) did badly after a resection of only 90 centimetres and one of Palmer (1914) had gross metabolic disturbances after 235 centimetres had been removed A similar length was excised from another patient who died soon afterwards in a state of inanition (Haymond 1935)

On closer examination it becomes evident that all cases in which metabolic deficiencies occurred after removal of less than one third of the small gut were complicated by other factors and so cannot be included in a valid discussion of the effects of resection *per se* This applies particularly to malignant neoplasms involving the small intestine and to regional enteritis (Crohn s disease) It is apparently agreed that the length of gut resected in a case of ileitis is of importance secondary to the possibility of continued spread of the disease to the remaining bowel (Kiefer and Arnold 1950 and the discussion following their paper) It is less well realized that any case in which a by pass is fashioned or a loop pocket or pouch produced may suffer metabolic disturbance on account of this condition entirely without relation to the length of intestine which may have been removed from the normal food circuit For instance cases of inadvertently formed gastro ileostomy develop deficiencies not from loss of absorbing surface but from the stagnating loop Haymond s patient (referred to above) suffered the formation of a 55 centimetre blind jejunal loop as well as excision of 235 centimetres and it is most likely that the loop offers the key to the progressive deterioration It seems to be the rule that resections of less than two thirds of the small bowel cause no serious metabolic disturbance unless complicated by other progressive disease or by a blind loop

**Conclusion**

One could therefore accept that resection of up to two thirds of small bowel will almost certainly be compatible with good health thereafter providing there

are no complicating factors amounts beyond this—up to resection of all but some *18 inches of jejunum or ileum—become increasingly dangerous*, but not necessarily disastrous If less than 18 inches are left death from inanition is likely If resection is to be performed for enteritis it would seem best to err on the side of extensiveness rather than the reverse (in order to prevent further spread) and not to fashion by pass loops

It does not seem to make much difference whether the remaining portion of small gut consists of jejunum or ileum either in man or in experimental animals (Berman et al 1947 Weckesser et al 1949 1951) although Jensenius (1945) and Kremen et al (1954) found that dogs withstood the loss of jejunum better than the loss of ileum Pietz (1956) has recently suggested that patients who have a portion of lower ileum remaining do better than those with a more proximal remnant of small bowel because of the importance of an intact ileo caecal valve

## THE REMAINING GASTRO INTESTINAL TRACT

**In man**

The remaining small intestine in man typically hypertrophies A second laparotomy on a patient revealed dilatation and atony (Barker 1905) and in a case reported by

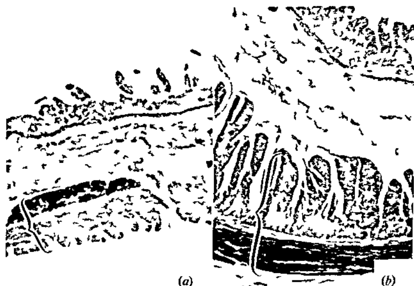



Fig 83 —(*a*) Section of jejunum near cut end of the removed segment (Toni) (1949) (*b*) section of jejunum near anastomosis from autopsy specimen (1952) Same magnification Thickening particularly of muscular layer (as indicated) (*B*) *courtesy of the Editor of* S Afr J clin Sci 1953)

West et al (1938) the small intestine was dilated and hypertrophied to the size of a normal colon Althausen et al (1949) reported upon a patient whose duodenum and 15 centimetres of remaining jejunum were anastomosed to the transverse colon 8 months after operation dilatation of the jejunum and coarsening of the mucosal pattern were seen In a second case Althausen et al (1950) reported marked dilatation of the distal jejunum

after resection of all but 2 feet of jejunum and ileum Lundberg (1920) found dilatation of the remaining small intestine in one of his patients by radiography and assumed this to indicate hypertrophy

In Toni autopsy revealed lengthening of the free margin of the duodenum and enlargement of rugae of the duodenum and of the remaining 6 inches of jejunum The muscle coat was twice as thick as that of the resected intestine (Fig 83) the remaining fragment of ileum was actually smaller than was believed to have been left at operation and histological evidence of hypertrophy was lacking Montgomery and Pincus (1955) reported the case of a female aged 23 years who was left with some 2½ feet and the dia meter of this remnant enlarged to three times the normal In no instance was obstruction a contributory factor

Among cases in men in which hypertrophy did not occur Denk s patient died of inanition 2½ years after resection of 540 centimetres of small gut for strangulated hernia atrophy of the remaining small intestine was found Shonyo and Jackson (1950) like wise reported no hypertrophy in their patient who survived for 1 year with only 4½ inches of small gut Shelton and Blaine (1954) reported similarly in their Negro patient who died 1 year after removal of all but 28 inches of small gut

**In experimental animals**

Since Senn s report in 1887 fairly numerous experimental resections have been made without striking unanimity in the morbid anatomical results A review of this work is given by Jensenius (1945)

Four out of six dogs operated upon by Monari (1896) survived for over 1 year but showed loss of weight absence of fat atrophy of the muscles and anaemia The mucous membrane of the remaining intestine was twice as thick as that of control animals the villi being larger and more numerous the circular muscle coat was thickened but not the longitudinal

Flint (1912) found particularly pertinent changes (Fig 84) At autopsy 3–18 months after the resection there was no lengthening of the small gut but a great increase in its transverse dimensions and the wall appeared twice as thick as the wall of adjacent gut removed at operation Inextensibility of the mesentery was held to explain the absence of lengthening The villi were increased in size but not in number Flint calculated that by this mucosal hypertrophy a 30 per cent remainder of gut would provide an epithelial surface equal to that of the whole original intestine The muscle especially the circular coat was markedly thickened The stomach and the colon were not hypertrophied and no changes in other organs were noted

Hypertrophy of the remaining gut was also found by Senn (1887) Nagano (1903) Soyesima (1911) and Stassof (1914) Both Flint and Stassof noted more marked hyper trophy in the jejunum than in the ileum similar to the findings in the case of Toni

On the other hand Trzebicky (1894) Wildegans (1925) and Jensenius (1945) did not find any hypertrophy of remaining intestine Jensenius made 20 resections of this kind and his observations appear to have been most thorough He was fully aware of the difficulties to be expected

Evans and Brenizer (1907) found that resection of up to 50 per cent of the jejunum and ileum resulted in recovery with hypertrophy of the gut whereas resection of over 85 per cent resulted in death from inanition without evidence of hypertrophy This may well be the clue to the above discrepancies for there may be a limit to the amount of intestine which can be removed and be followed by hypertrophy and this limit may vary considerably from individual to individual

**The large intestine**

The large bowel does not appear to take over any of the functions of the resected small gut nor is any adaptive change in histological appearance reported It is known

that certain nutrients mainly sugar and probably amino acids (Rhoads et al 1939 Brezin and Oren 1954) can be absorbed through the colonic mucosa and it seems quite likely that this function becomes useful in cases of massive small bowel resection In the case of Toni the glucose tolerance curve was flat with a delayed rise and no excessive loss of carbohydrate was noted in the stool This suggested that the colon actively absorbed sugar On the other hand patients who have undergone excision of the large

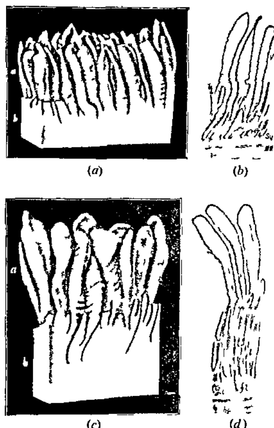



Fig 84 —Showing the hypertrophy of the intestinal villi following massive resection of the small intestine in dogs (*a*) and (*b*) are from the upper end of the excised intestine (*c*) and (*d*) are from the adjacent portion of the remaining intestine 18 months later (*After Flint J M and by courtesy of the Editor of* Bull Johns Hopk Hosp )

bowel in addition to much of the small bowel appear to suffer no increased loss of carbohydrate

Certainly the large bowel appears to increase its efficiency as a reservoir in that the diarrhoea which always follows massive resection usually slowly diminishes until the patient may actually have only a single bowel action daily Admittedly careful dietary regime and reduced transit time through the rest of the gastro intestinal tract may also help to reduce the diarrhoea Secondary colitis has not been reported

**The stomach**

The stomach like the large bowel cannot take over the function of the small intestine In Toni free hydrochloric acid was reduced and finally absent despite caffeine stimulation pepsin remained present Althausen et al (1949) curiously reported free hydrochloric acid but no pepsin in one of their patients

**The transit time**

The transit time has been stated to become lengthened in certain cases (second case of Shelton and Blaine 1954 experimental dogs of Clatworthy et al 1952 and of Stassof 1914) In general however injected material reaches the colon very quickly—in the case of Toni the head of a barium meal was in the caecum within 15 minutes in the patient reported by Brezin and Oren (1954) (12 inches of jejunum left) it was in mid-colon within 5 minutes

## THE FAECES

The faeces tend in time to become less fluid and less frequent though usually diarrhoea may readily be precipitated by mental upset or dietary indiscretion With a diminution in number of stools their size may become enormous Toni s record was the production of 5 litres in a single effort Early writers commented upon increased putrefaction in the colon usually diagnosed by the presence of indican in the urine On the other hand Jackson and Linder (1951a) were struck with the lack of odour of Toni s massive pale stool and found an almost total absence of indole and skatol therein Six specimens were cultured bacteriologically and none grew Proteus Aerobacter or Clostridia

**Reaction**

Toni s faeces were always acid with a *p*H between 3 5 and 6 (Hawk et al 1947 gave figures of *p*H 7–7 5 for normal adult stool) Titration of samples to *p*H 7 4 showed that some 950 millilitres of 0 1 N alkali per day were necessary to neutralize it This loss of acid however was not sufficient to produce systemic alkalosis The excessive acidity could be accounted for by absence of alkaline succus entericus reduction of pancreatic secretion (*see below*) and free fatty acids excretion No similar investigations appear to have been reported by other authors

Fat protein and carbohydrate in the faeces are considered under the heading of Intestinal Absorption on page 250

## PHYSICAL STATUS

Loss of weight often gross and precipitous is to be expected following massive resection even in patients who ultimately do very well Thus the second patient of Jackson and Linder (1951b) reduced from 115 to 65 pounds following excision of two thirds of the small gut She recovered a weight of 78 pounds in 10 weeks and later was back at the pre operative figure Montgomery and Pincus (1955) reported on a patient who left with 2¼ feet gained in weight from 90 to 115 pounds despite an intervening pregnancy Even patients who do badly almost always start gaining weight after their first few weeks loss Toni (with 7 inches of small intestine) dropped from 140 to 87 pounds and regained to 102 pounds the first patient of Shelton and Blaine (1954) dropped from 128 to 110 and then back to 118 pounds dying after 1 year the second patient of Uricchio et al (1954) with 6 inches remaining from 150 to 73 pounds back to 99 pounds in 5 months

Apart from pure inanition other secondary physical syndromes have been comparatively infrequently reported—they include anaemia oedema avitaminosis B scurvy and tetany and are considered later in their appropriate sections

## MENTAL STATUS

Massive resections have several times led to changes in personality which are reminiscent of those occurring in simple under nutrition or starvation as in

prisoner of war camps and in the experiments of Keys et al (1950) who reported irritability self mutilation and even hypomania in their volunteers A patient of Palmer (1914) developed a psychosis but his state is not reported in detail Uricchio s second patient became apprehensive and combative and refused to eat Martin s patient was *demanding exacting and moody but only in the case of Toni* is the mental state analysed in detail (Berman 1951) Almost one year after his operation this patient had four epileptiform fits These ushered in a psychosis which consisted essentially of marked disturbances of affect with deep depression and suicidal ideas bizarre behaviour with hallucinations and delusions largely of a persecutory type He was being treated at this time for skin changes of a pel lagrinous nature but parenteral nicotinic acid riboflavin aneurin pyridoxin and ascorbic acid in heroic doses had no effect on the mental state although the cutaneous manifestations of deficiency cleared up It might be suggested that the psychological changes were related to those which occur in children who suffer from the protein malnutrition known as kwashiorkor but intravenous amino acids although associated with a gain in weight did not ameliorate the mental disturbance

In experimental dogs Petri et al (1942) and Jensenius (1945) have described gross degenerative changes in the entire central nervous system but there appears to be no human counterpart to these findings after intestinal resection Careful post mortem examination of Toni s brain showed no obvious histological changes

## INTESTINAL ABSORPTION AND DIRECT BIOCHEMICAL EFFECTS OF ITS DEFICIENCY

Evidence can be presented for diminished absorption of *all* substances *except* alcohol following massive resection Within a matter of weeks following the opera tion however there is a tendency to improvement in absorptive capacity The diminution of diarrhoea indicates improved water absorption and the regaining of weight shows that the absorption of total calories improves More exactly Wildegans (1925) found considerable recovery in fat and nitrogen absorption in dogs while Althausen et al (1950) in two patients clearly demonstrated an improve ment in absorption of sugars fats and amino acids using tolerance curve tech niques It is interesting to note that in a patient studied by Martin et al (1953) whose jejunum and ileum were completely excised there was no recovery of weight and a progressive diminution of absorptive capacity for nitrogen to judge from the data presented Regarding total calories Althausen et al (1949) reported on a patient who appeared capable of absorbing a maximum of 1 000 calories 10 months after removal of all but 10 inches of jejunum Toni was able to absorb 1 800 calories almost entirely of carbohydrate origin

In general the lack of success with pre digested and synthetic diets and particu larly the experiments of Althausen et al (1949) suggest that failure of absorption after resection is far more important than is failure of digestion Reports frequently remark upon a high degree of splitting of the faecal fats Nevertheless Toni s stool always contained totally undigested food particles of all types

### *Fats and fat soluble vitamins*

It is generally agreed that the absorption of fats is the most impaired Toni s worst performance was the absorption of only 5 per cent of the intake Fat

balance studies in other patients uniformly indicate defective absorption Even the patient referred to by Jackson and Linder (1951b) with some 6 feet of small gut remaining lost 10 per cent of her small intake of 40 grammes Fat and butter tolerance curves provide similar evidence showing little or no rise in the plasma level after large oral feeds (Jackson and Linder 1951a Althausen et al 1950)

The serum carotin and vitamin A are markedly low (Althausen et al 1949 Jackson and Linder 1951a) and the vitamin A tolerance curve is flat although Toni s absorption of this vitamin appeared considerably better than that of Althausen s patient No report of specific clinical evidence of vitamin A deficiency has been found

Prolongation of prothrombin time has been reported (Althausen et al 1949) and *was taken to indicate a gross deficiency in vitamin K absorption*

It is difficult to assess the efficiency of vitamin D absorption since its requirements are in any case small in the adult and vary according to the available sun light Osteomalacia does not appear to have occurred even in the case quoted by Montgomery and Pincus (1955) who withstood two pregnancies Toni s serum phosphorus was markedly depressed and radiographs of his femur showed some decalcification after 3 years but wide osteoid seams were not remarked upon at autopsy

It is generally assumed that restriction of fat intake is beneficial from the point of view of general absorption Actually there is little direct evidence for this The figures given by West et al (1938) do not show any improvement in absorption of fat and of other foodstuffs on reducing the fat intake On the other hand the metabolic balance data of Jackson and Linder (1951a) in their patient Toni demonstrate a distinct advantage from reducing the fat intake from some 170 grammes (which was his natural choice) to some 40 grammes The total fat absorbed remained the same the percentage fat absorption trebled The nitrogen absorption rose over 10 per cent (from 30 to 40 per cent) and the total calories absorbed rose from some 1 600 to nearly 1 800 The percentage utilization of the caloric intake rose from 45 to 73 per cent On the other hand Nocker (1955) claims that his patient s percentage absorption of fat actually improved on a high fat intake Bothe et al (1954) also reported a patient who appeared to improve

Measurements of serum cholesterol are not often recorded but in several cases were definitely low (78 milligrams per 100 millilitres in Toni in whom a serial fall was demonstrated 100 milligrams in the patient of Martin et al 1953)

**Protein**

There is general agreement that absorption of nitrogen is impaired in the more massive resections but to a lesser extent than that of fat Toni was able to absorb only some 40 per cent of his ingested protein which put him very near the border line of protein under nutrition *per se* (Leitch and Duckworth 1937) Other reported cases have done better than this except that of Berman (1951) and Martin et al (1953)

Metabolic balance studies frequently show the patient to be in balance for nitrogen or even actively retaining it (corresponding to the period of weight gain) It must be pointed out however that nitrogen balance does not mean nitrogen sufficiency and nitrogen retention may actually be a measure of tissue avidity resulting from chronic protein deficiency (Peters 1948)

Perhaps because the defect in nitrogen absorption is only of moderate degree the plasma protein level is not usually reduced after resection In fact low plasma protein has been found only terminally and only in cases of the most massive resection when oedema may also appear (Martin et al 1953 the first patient of Weckesser et al 1949 Linder et al 1953)

Creatinuria high serum creatine and low creatinine co efficient (milligrams of urinary creatinine per kilogram per day) have been found (Toni) indicating abnormality of muscle metabolism and generally diminished muscle mass (Hunter 1928)

**Carbohydrate**

It is usually stated that carbohydrate absorption is virtually complete a statement which appears to be at variance with the marked flattening of oral glucose tolerance curves as described by Althausen et al (1949 1950) Kositchek and Rabwin (1950) Christensen et al (1950) and Jackson and Linder (1951a) Althausen claims that increased bacterial fermentation in the colon may render the unabsorbed carbohydrates undetectable by ordinary methods and so suggests that a lack of carbohydrate in the stool is of no value in indicating full absorption Certainly some bacteria are capable of forming triglycerides from carbohydrates in the colon an effect which would increase the apparent loss of fat in the stool *and decrease the loss of carbohydrate In any event there can be no doubt that* the more severely deprived patients depend almost entirely upon carbohydrate for their calories and it is fortunate that these are absorbed with comparative ease

**Calcium and phosphorus**

Althausen et al (1949) and Jackson and Linder (1951a) found persistent moderate negative calcium balance in their patients though in both instances the serum calcium remained normal and tetany did not occur It is often stated that low serum calcium and tetany are expected concomitants of the post resection state but this is not borne out on careful examination of the literature In patients where resection was not complicated by other factors hypocalcaemic tetany is rarely reported (West et al 1938 Cosh 1944 Shelton and Blaine 1954) In the case reported by Weckesser et al (1949) there was a terminal drop in serum calcium while Palmer (1914) reported on the occurrence of tetany in the post operative period but later a positive calcium balance was found Althausen et al (1950) *found that tetany was a temporary phenomenon in their first case Pincus (1951)* reported that tetany did not occur in his patient even during her two pregnancies Althausen et al (1949) suggest that West s patient lost excessive amounts of calcium because of the high fat diet he insisted on taking

The serum phosphorus is not usually affected in Toni it was low at one stage normal terminally in this patient the alkaline phosphatase level also dropped as it often does in pure under nutrition

**Potassium sodium, and chloride**

Excessive faecal loss of potassium sodium and chloride has been found (Jackson and Linder 1951a Spencer et al 1953) and low serum potassium reported (Linder et al 1953 Rawson 1953 Shelton and Blaine 1954) Rawson compares this with the hypokalaemia of starvation (Howard 1946) Jackson and Linder

found also a very high urinary excretion of chloride in Toni again reminiscent of pure under nutrition (Keys et al 1950) It is interesting to note that Toni developed a greatly increased desire for salt which perhaps compensated for his excessive total excretory loss of some 18 grammes a day

**B vitamins**

*Thiamine*

Vitamin $B_1$ deficiency has not been reported and Althausen et al (1949) found a normal blood thiamine chloride level

*Pellagra*

Pellagra seems to be rare but it occurred in Toni and in the case reported by Martin et al (1953) Toni also exhibited angular stomatosis hyperkeratosis and glossitis and these cutaneous manifestations responded very slowly to parenteral vitamin B therapy

**Vitamin C**

Scurvy (Nocker 1955) appears to be a rare complication of resection although Althausen et al (1949) and Jackson and Linder (1951a) found low or absent plasma ascorbic acid and grossly depressed absorption of this vitamin These authors remark that this is interesting in view of the chemical simplicity of this water soluble compound and the ease with which it is usually believed to be absorbed

**Alcohol**

Jackson and Linder (1951a) found that Toni s absorption of the alcohol contained in 4 ounces of brandy was normal as judged by the blood levels achieved No other similar reports are available

## OTHER EFFECTS

**Basal metabolic rate**

Very low basal metabolic rates have been found after resection (Jackson and Linder 1951a (in Toni) Martin et al 1953) It is easy to consider a reduction in the basal metabolic rate as a compensating measure for the conservation of energy and the same phenomenon is found in pure under nutrition (Lusk 1921) However as Keys and Brozek (1953) point out the great reduction in active body mass (especially muscle) which occurs in these circumstances renders the ordinary method of correction of the basal metabolic rate quite inaccurate

**Blood vascular state**

*Hypotension*

Hypotension has been noted in a few of the most massive resections (Althausen et al 1949 Martin et al 1953) while Toni s electrocardiographic deflections were of low voltage

The heart muscle at autopsy has shown atrophy increased connective tissue and vacuolation of cells

*Blood volume*

The circulating blood volume measured by the Evans blue dye test was found to be greatly reduced in the patient observed by Brezin and Oren (1954) but was actually high in Toni

*Anaemia*

Anaemia despite many statements to the contrary is not a common nor a significant finding after massive resection In most reported cases the haemoglobin is normal though a hypochromic anaemia of moderate degree may be a late or terminal finding (Weckesser et al 1949 Martin et al 1953 Linder et al 1953) Marked anaemia is a well known occurrence after the formation of loops or strictures in the small gut when it is often macrocytic and megaloblastic (Barker and Hummel 1939 Watson et al 1948) and it is evident that many authors have not distinguished between intestinal resection and intestinal exclusion or loop formation Despite a considerable amount of work on the subject megaloblastic anaemia has never been shown to follow clinical or experimental small bowel resection (Miller and Rhoads 1937 Petri et al 1942 Jensenius 1945 Weckesser et al 1951)

Krevans et al (1956) however demonstrated a gross diminution in absorption of $^{60}$Co labelled vitamin $B_{12}$ by the Schilling technique in two cases of massive resection so that the development of megaloblastic anaemia in such patients would appear to be merely a question of time Nevertheless in the few reported cases with 10 or more years post operative follow up anaemia has not been a feature (for example Matthaei 1925 Jerauld and Washburn (1929) whose patient was well after 22 years Jackson and Linder 1951b Croot 1952) It seems plain that there is some additional factor besides time to account for the facility with which pernicious anaemia develops in loop and stricture cases and its rarity following resections

*Iron deficiency*

The serum iron level was normal in Toni Indeed pure iron deficiency from nutritional lack would seem unlikely in a male Furthermore it is probable that iron is absorbed largely by the duodenum (Cartwright 1947)

**Water metabolism**

The ability to absorb water appears usually to increase with time as the stools become less fluid and less frequent Little work has been reported on other aspects of water metabolism Toni was able to absorb water but could not produce a water diuresis despite a considerable increase in the extracellular fluid space as measured by the thiocyanate method Intravenous fluids likewise failed to cause a diuresis furthermore Toni consistently maintained a relative nocturnal diuresis All these features are characteristic of severe simple under nutrition as was seen in prisoner of war camps (McCance 1951) Partial adrenocortical depression or an excessive production of pituitary antidiuretic factor (Gopalan 1950) may have played a part

**Renal function**

No reports have been seen which give clinical or histological evidence of renal damage *The glomerular filtration rate was greatly diminished in Toni* but this may be explained by the very low protein absorption (Goldring et al 1934)

**Pancreatic function**

Jackson and Linder (1951a) found by duodenal intubation studies that Toni developed deficiency of exocrine function with poor production of alkali and enzymes This was later confirmed at autopsy (Linder et al 1953) when gross *pancreatic atrophy* and connective tissue replacement were found (Fig 85) It

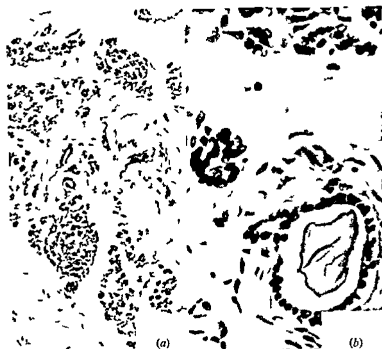



FIG 85 —(a) Pancreas showing gross atrophy with increase of loose connective tissue *Parenchymatous cells are small (low power)* (b) showing inspissated secretion lying in a duct (high power) Figs 85 and 86 illustrate tissues removed at autopsy from case whose intestine is illustrated in Fig 83 (after 3½ years with 6–7 inches of jejunum and ileum) (*By courtesy of the Editor of* Metabolism)

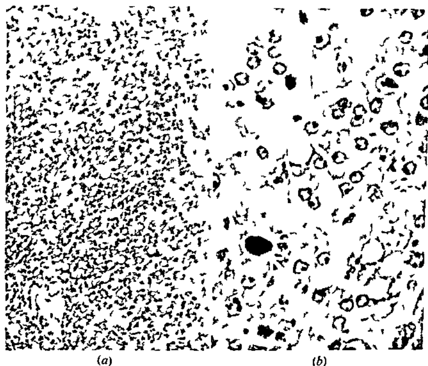
was considered that this was caused by the combined effects of dietary insufficiency especially with regard to protein and lack of the pancreas stimulating hormones secretin and pancreozymin

It is unfortunate that no other studies of pancreatic function following intestinal resection have been made since the changes mentioned above resemble so closely those found in infantile malnutrition and kwashiorkor (Davies 1948 Waterlow 1948 Veghelyi 1950 Jackson and Linder 1953)

**Hepatic function**

There is little to be found concerning hepatic changes after intestinal resection although *prolonged under nutrition especially with the very high effective*

carbohydrate preponderance (Best et al 1949) would be expected to cause at least fatty damage Experimental dogs have shown no consistent changes while hepatic function tests in patients have largely been normal At autopsy Toni (3½ years



(a) (b)

Fig 86 —(a) Liver showing marked fatty change (low power) (b) showing fat bile thrombi (arrow) and stippling of cells due to haemosiderin (high power)

after his resection) had a grossly fatty and atrophic liver (Fig 86) while Martin et al (1953) report a hepatic atrophy without a fatty infiltration in their patient

**Endocrine function**

*Pituitary body*

Depression of pituitary function is indicated by the low urinary gonadotropins in the case reported by Martin et al (1953) and may account for amenorrhoea (Pincus 1951) and the possible adrenal hypofunction (hypotension and salt abnormalities) lowered basal metabolic rate and sexual deficiency

*Sex function*

Toni gradually lost his libido erections ceased 17 ketosteroids were low (as in Martin s patient) and at autopsy there was virtually no spermatogenesis (*see* Petri et al 1942) Secondary sexual characters were not affected

The endocrine status is compatible with that found in simple under nutrition gross deficiency does not occur Two pregnancies have been reported in a woman

who had only 2½ feet of small intestine during which there was actually an improvement in her physical state (Montgomery and Pincus 1955)

## TYPE OF DEFICIENCY SYNDROME PRODUCED

Bennett and Hardwick (1940) introduced the term jejuno ileal insufficiency to cover the sprue like syndrome produced by various diseases affecting the small gut which would include that caused by the production of loops exclusions or by passes There are many reasons for believing that the symptoms which arise are not caused by simple loss of intestinal absorptive capacity (Jackson and Linder 1951b 1955) Simple loss of small bowel by operative removal does not produce this *jejuno ileal insufficiency state as can be seen by the rarity with which* megaloblastic anaemia hypocalcaemic tetany and hypoproteinaemia develop

Lack of understanding of this principle has led to the consideration of symptoms being due to resection which were far more likely caused by the presence of a stagnating loop (Haymond 1935 Mayer and Criep 1949 Berg and Freuger 1955)

In fact massive resection characteristically produces a syndrome of under nutrition with special adaptation closely allied to pure starvation In summary this may be evidenced by the following changes

(1) Rapid reduction in weight particularly muscle
(2) Fall in basal metabolic rate and in blood pressure
(3) Loss of libido low 17 ketosteroid excretion and testicular atrophy Pituitary and (?) adrenal hypofunction Amenorrhoea
(4) Increased desire for salt (excessive salt loss in stool and urine)
(5) Maintenance of serum calcium and phosphorus (? by draining body stores) ? Increased avidity of bones for calcium (Spencer at al 1953)
(6) Diminution of protein katabolism (low creatinine production low blood urea low urinary nitrogen)
(7) Hypertrophy of epithelium and muscle of remaining small bowel
(8) Ability of colon to accommodate large stool masses ? Increased absorption of sugar and amino acids by the colon (Althausen et al 1949 Brezin and Oren 1954)
(9) ? Delayed transit time in gastro intestinal tract

Less helpful features but also characteristic of simple under nutrition are as follows

(10) Vitamin deficiencies low blood vitamin levels
(11) Mild hypochromic anaemia
(12) Psychological deterioration
(13) Increased extracellular fluid space terminal low plasma protein and oedema.
(14) Nocturnal polyuria and inability to produce a *water diuresis*
(15) Hypokalaemia (excessive loss of potassium in stool and ? urine)
(16) Hypocholesterolaemia (? reduces liability to atheroma)
(17) Depressed glomerular filtration rate
(18) Pancreatic exocrine failure and tendency to liver atrophy

## MANAGEMENT AFTER MASSIVE RESECTION

### Diet

It would seem best to reduce the daily fat intake to 30–40 grammes Frequent small meals of high protein and high-caloric content should be taken It is doubtful

whether there is any value in ordering special easily digested foods while synthetic diets including amino acids pure sugar and cream have proved unhelpful High roughage foods and stewed fruit should be avoided An enormous intake of milk together with much cheese and butter (also kaomagna paregoric and metamucil) apparently helped to produce a gain in weight in a patient left with 21 centimetres of small gut (Bothe et al 1954) So successful in forcing in calcium was this regime that the patient developed a staghorn renal calculus Papain is recommended by Pietz (1956)

**Supplementary vitamins**

Added vitamins in high dosage are plainly indicated but in the more severe cases they may need to be given parenterally It is probably advisable to supplement the iron and calcium intake also

**Intravenous supplements**

Amino acids may be distinctly useful in producing a small gain in weight but the real need would appear to be for intravenous fat boosters when this product becomes available Tween 80 an emulsifying agent has not been found helpful in promoting fat absorption (Christensen et al 1950 Shelton and Blaine 1954 and the discussion following)

**Constipating agents**

Opium bismuth Pectocel paregoric chalk and the intestinal movement dampers such as Banthine may be tried particularly to control the diarrhoea A patient with no small intestine produced a single stool daily while under the influence of 50 milligrams of Banthine six hourly (Martin et al 1953) Experimentally vagotomy performed soon after the resection increased the fat absorption (Weckesser et al 1951)

**Testosterone**

Testosterone was employed successfully by Pincus (1951) whose patient started on the propionate and was eventually maintained on only 5 milligrams of methyl testosterone a day Nitrogen retention was rapidly produced with later increase in weight serum albumin cholesterol and fasting blood sugar Normal menstruation was re established a diminution in stool output was a concomitant feature and one may wonder whether this was not perhaps the most important factor in the improvement

## INTESTINAL RESECTION IN SPECIAL CIRCUMSTANCES

**Complications due to partial gastrectomy**

Several patients have been described who suffered partial gastrectomy followed by massive resection (Rawson 1953 Weckesser et al 1949 Croot 1952 Johnston and Reagan 1952 Shelton and Blaine 1954) Although death occurred after a few months in three of them it is difficult to say whether the added loss of the stomach was in any way responsible

**Resection during active growth**

There have been few reported instances of massive resection in childhood when it is more likely to be necessitated by intussusception torsion around persistent

ducts or duplication with torsion (Benson and Sharp 1950) At least 3 patients have done well (Blayney 1901 Flint 1912 Ruggi quoted by Jensenius 1945) Flint (1912) and later Petri et al (1942) found that young puppies did poorly On the other hand Clatworthy et al (1952) specially investigated this subject and claimed that young dogs did well and grew satisfactorily even after removal of 80 per cent of the small bowel

**Complications due to pregnancy**

Montgomery and Pincus (1955) reported a patient who actually improved during each of 2 pregnancies No other similar case has been found

**Correction of obesity**

Henrikson performed small bowel excision to correct obesity but was unable to control the amount of weight lost Following this Kremen et al (1954) excluded great lengths of jejunum and ileum with the idea of replacing segments if necessary Knowledge of the loop syndrome would indicate the great danger of such a procedure

**In treatment of ascites caused by portal hypertension**

Resection of large tracts of small gut would considerably diminish the size of the portal vascular bed and so acting similarly to a porto-caval shunt might reduce the tendency to ascites in cases of portal hypertension Success has been reported to have followed the operation in a patient of Fuller et al (1937) and in experimental dogs (Bernhard et al 1953)

## RESECTION OF LARGE INTESTINE ONLY

Metchnikoff (1903) believed that the colon was the enemy of mankind—a sump *full of iniquitous absorbable digestive products Lane (1908 1913) acting on such* a belief used to resect this organ for cases of severe constipation There was a considerable operative and post operative mortality (Bainbridge 1913) but the remaining patients seemed little the worse for their loss Hurst (1919) feared that such persons would suffer more seriously from poisons like lead and from uraemia since the colon can excrete lead and some of the metabolites which accumulate in the blood in renal failure Hurst also believed that people after colectomy were excessively sensitive to morphine none of these suggestions appears to have been substantiated

The most obvious function of the large bowel is its action as a reservoir for faeces which during their sojourn in this chamber lose water and become firmer and more malleable and so able to appear as the familiar sausage shaped excreta It is therefore to be expected that a degree of looseness of the bowels will follow colectomy This was apparently not seen after the operation for constipation but softish motions 3–4 times a day are usual after colectomy in other cases (Lockhart Mummery 1923) After some years however bowel actions may become quite normal—a fact probably related to an interesting observation by Keith (1915) that the small gut shortens and dilates after a colectomy and eventually *comes to resemble the large bowel*

It is interesting to contrast our first patient Toni with our second patient

whether there is any value in ordering special easily digested foods while synthetic diets including amino acids pure sugar and cream have proved unhelpful High roughage foods and stewed fruit should be avoided An enormous intake of milk together with much cheese and butter (also kaomagna paregoric and metamucil) apparently helped to produce a gain in weight in a patient left with 21 centimetres of small gut (Bothe et al 1954) So successful in forcing in calcium was this regime that the patient developed a staghorn renal calculus Papain is recommended by Pietz (1956)

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Miss B T (Jackson and Linder 1951b) Toni whose large bowel was intact usually produced but one stool a day despite the loss of his small gut albeit a stool of elephantine proportions, whereas Miss B T with no nutritional dis turbances from her small plus large intestinal resection had 4–5 bowel actions daily The more frequent passage of softer stools would appear to be the only physiological effect of large bowel resection

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that the permanent presence of foreign particulate substances may create an area of oedema with subsequent fibrosis

The two types of experiment are more mutually supportive than they are antagonistic for such particles after ingestion by the intestine may find their way into the lymphatic vessels and become arrested in the nodes The obstructive influence of the reaction they cause would tend to hamper resolution of the swollen intestine even if it could not be held as the primary cause of the disease

It is pertinent to comment that certain brands of tubed tooth paste on sale at the present time contain silica or talcum powder or other similar substances and that a number of young teenagers found to have Crohn s disease prove to be lavish tooth paste users

### *Tuberculosis and sarcoid*

The theory that Crohn s disease is of a tuberculous nature seems to be disproved by two factors (1) caseation does not occur either in the thickened intestinal wall nor in the swollen lymph nodes and (2) the presence of the tuberculosis bacillus cannot be demonstrated

Frank tuberculous enteritis in which the ileum has the appearance at operation of the ileum in Crohn s disease may however occur (Fig 87) Furthermore there is a very close clinical association between phthisis and granulomas of the caecum in which the morbid anatomy is identical with that of Crohn s disease It would be unwise therefore to deny the possibility that the disease may in some cases be an unusual manifestation of tuberculosis

The sarcoid theory (Hadfield 1939) may now be discounted because despite observations carried out over periods of 10 years and more there is no evidence that generalized sarcoidosis ever develops in patients known to be suffering from Crohn s disease and negative results to the Kveim skin test for sarcoidosis have been reported (Crohn and Janowitz 1954)

### *Acute ileitis*

It is very doubtful if acute ileitis is a related disorder though it is fully recognized that the stage of onset of Crohn s disease may be extremely short rapidly developing into an acute abdominal condition for which exploratory operation is often performed on a diagnosis of acute appendicitis with abscess formation There is little evidence that acute mesenteric adenitis associated with a pink terminal ileum—sometimes found in infants and young children at operation for suspected appendicitis—is an antecedent cause

### *Social status race and familial predisposition*

There is little evidence that the incidence of Crohn s disease is related to social status and apart from a suggestion that Jews may be more liable than Gentiles no marked racial predisposition has been established

Many examples of the disease occurring in members of the same family suggest the possibility of genetic or environmental predisposition (Heard and John 1956) The author s patients have included female twins aged 27 years and 30 years respectively at operation and two brothers aged 22 and 28 years at operation

# CHAPTER 17

# CROHN'S DISEASE AND RELATED CONDITIONS

HAROLD C EDWARDS

## Introduction

THE term Crohn s disease is used to denote a non specific inflammatory condition affecting the terminal ileum and ceasing at the ileo caecal valve Pathological states of similar morbid anatomy occurring in other parts of the alimentary tract are treated under the heading of related conditions The reason for this somewhat arbitrary grouping is that Crohn s disease as thus interpreted is a distinct clinical entity

## CROHN S DISEASE

### Aetiology

*Foreign body ingestion and lymphatic obstruction*

Changes in the terminal ileum identical with those of Crohn s disease have been produced in animals by feeding them on various particulate substances or by causing obstruction to the lymphatic vessels by interference with the appropriate lymphatic nodes Chess et al (1950) by feeding dogs on talcum powder and finely divided sand and rats on sand for a sufficient period of time and in sufficient quantity were able to produce the changes not only in the terminal ileum but also in the related mesenteric lymph nodes

The attempt to produce the disease by blocking the lymphatic drainage of the bowel was made because the intense lymphatic oedema in the submucosa of the affected ileum which may be an early feature of the disease suggested that lymphatic obstruction may be the primary cause and ulceration and subsequent fibrosis secondary to it in other words that the disease is a primary affection of the mesenteric lymph nodes in the ileo caecal angle The concept is supported by the macroscopic changes in the intestinal wall being often sharply demarcated The occasional finding of a short length of unaffected bowel in the middle of the diseased area would also agree well with the concept

The method adopted by Reichert and Mathes (1936) was to inject substances such as silica bismuth oxychloride rose aniline dye and sodium morrhuate alone or in combination into the mesenteric and serosal lymphatics In some of the animals a culture of *Bacillus coli* was administered intravenously 3 hours before injection of the sclerosing agent and it was noted that the bowel changes were more marked in the animals so treated

A weakness of this otherwise plausible theory is that the lymphatic glands are not always involved to any serious degree in Crohn s disease particularly in the more chronic and fibrotic type occurring in older people Zetzel (1956) considered that a further reason for not accepting the theory is that in acute lymphadenitis the small intestine is only rarely involved

Nevertheless both types of experiment produce such an impressively faithful pathological replica that their implication merits careful examination Both show

dormant for many years and has been known to recur 20 years after an apparent cure by operation The disease may resolve completely in its early stages or with a legacy of permanent fibrotic change in the bowel which is not incompatible with good health Finally its course may be profoundly influenced by emotional stress

Great emphasis is placed upon the importance of the early recognition of the disease in the young subject for appropriate medical care may thwart the tendency to irreversible changes in the bowel wall and will in any case do much to slow down the progress of the disease

It is convenient to describe three clinical phases (1) onset (2) physical signs and (3) complications Since diagnosis from physical signs and complications is a simple matter attention is focused upon the mode of onset Despite the vagaries of the disease and its insidious nature a clinical pattern becomes discernible after study of the early history of a series of patients

*Phase of onset*

An adolescent or young adult of slight build alert mind sensitive nature and active habits starts to suffer mild abdominal discomfort associated with an increasing tendency to diarrhoea The appetite becomes impaired there is perhaps a slight loss of weight and in female patients the menses may become scant or irregular

The patient tires easily suffers from bouts of depression and powers of concentration become diminished Apart from a minor degree of anaemia and perhaps a raised erythrocyte sedimentation rate with a slight rise in temperature investigation including radiological examination is negative There is some danger at this stage that nervous dyspepsia will be diagnosed and the patient subsequently be treated solely by psychiatric means or that the patient be submitted to operation with a diagnosis of grumbling appendix Such an undertaking is not necessarily harmful provided the surgeon is alive to the danger of appendicectomy for it will provide a positive diagnosis particularly if a lymphatic gland is removed for microscopic examination Suspicious radiological findings may sometimes precede the appearance of physical signs In themselves they pass unnoticed but taken in conjunction with a history as described are to be regarded as significant

Such a march of events is of course by no means the rule In some patients particularly amongst the later age groups the disease process may be associated solely with a fibrosis within the terminal ileum with the development over a number of months of symptoms and signs of chronic obstruction or particularly in young subjects it may be a very acute process from the start a severe illness developing with great rapidity The first sign in 3 of the author s patients was acute ileus At any stage of the disease including the phase of onset an acute peri anal abscess may develop leading to fistula (page 267) as was noted in the case histories of 6 patients of ages ranging between 21 and 26 years before the diagnosis of Crohn s disease was established Its occurrence in association with a history of diarrhoea in young people should therefore be regarded as an important pointer to diagnosis The abscess is probably due to infection in the crypts of Morgagni and is associated with the frequency of stool According to Crohn the significance of peri anal abscesses and fistulas has not been sufficiently appreciated He expresses the opinion that suppurative peri anal fistulas in the presence of diarrhoea indicate

*Personality*

Crocket (1952) believes in the existence of a personality factor His sketch of personality *emphasizes the possession* of virtuous qualities—sensitivity intelli gence high moral principles co operation courage to which may be added



FIG 87—Primary tuberculo sis of the small intestine in a male aged 34 years (autopsy *specimen)* Emaciated *with* high pyrexia ascites oedema of legs and finger clubbing Laparotomy 18 7 47 5 feet of ileum involved Short *circuit* no *improvement* Patient died 8 9 47 from massive pulmonary embo lism Histology showed gran ulation tissue in the wall of the bowel with caseation and subserosal miliary tubercles Mesenteric glands enlarged but not caseating Tuberculous nature con firmed by guinea pig in oculation

patience and loyalty Crocket was not so convinced as to the positive part that may be played by emotional stress but all clinicians will be able to quote instances from their own case books in which severe emotional experiences appear to have provoked the disease and others in which pre existing disease has been aggravated thereby

**Clinical features and diagnosis**

Crohn s disease varies greatly in its clinical manifestations It may present in the form of an insidious fibrotic process without gross lymphadenoid change or it may develop rapidly with emphasis chiefly on mucosal changes accompanied by great swelling of the lymphatic nodes and causing an acute febrile illness Its behaviour follows no formal pattern It may progress continuously and with increasing momentum or fitfully with periods of relative quiescence It may lie

continue so for weeks Occasionally it may reach an even higher level In one such case it pursued an unusual course suddenly falling to normal for no accountable reason at a time when a surgical procedure was contemplated

*Phase of complications*

Symptoms of intermittent chronic obstruction may predominate particularly in older patients or late in the course of the disease and be associated with visible peristalsis Surgical relief is required There should be no urgency about operating for the milder symptoms of obstruction associated in younger people during the second phase for attacks in such cases may subside during conservative tre itment It has been found by experience however that if the symptoms of obstruction are at all marked during this stage surgery will eventually be needed Occasionally the patient may develop obvious acute obstruction which should be treated in the first instance by intubation Ileostomy is to be condemned

*Fistula*—The mechanism of fistula formation is not clear It is not due to abscess formation as in diverticulitis but is more probably due to lysis of the sodden ileal wall and spread of the process to an adherent operation scar or to a neighbouring hollow organ

*External abdominal fistulas* may be single or multiple and were noted in 12 of a series of 51 patients This figure exceeds the usual incidence recorded but matches that of Brown and Donald (1942) of 47 in 178 cases

It is very rare for fistulas to occur except through a previous laparotomy scar No single case was encountered in Crohn s 562 patients One example in a woman aged 22 years was observed it developed during conservative treatment for what was considered to be an abscess on the appendix but which was found at subsequent operation to be a typical example of Crohn s disease (C E P Markby)

The fistulas usually develop during convalescence after exploratory operation There is reason to believe that appendicectomy encourages the formation of fistulas and in view of this it cannot be too strongly emphasized that appendicectomy should not be performed Such development and persistence of a fistula after appendicectomy may occasionally be the first indication of the nature of the disease

The presence of an external fistula is normally to be regarded as an indication for surgery for spontaneous healing is exceptional

*Internal fistulas* are most commonly found leading into the ascending or transverse colon Occasionally the sigmoid colon is involved and very rarely the rectum No neighbouring hollow viscus is exempt and examples of fistula into the uterus a fallopian tube a ureter and even the duodenum have been recorded One of the author s patients suffers from an ileo recto vaginal fistula

*Peri rectal and peri anal fistulas* Attention has already been called to the significance of peri anal abscess leading to fistula occurring at an early stage in the history of the illness The reported over all incidence varies from 18 per cent (Penner and Crohn 1938 Crohn 1949) to 31 6 per cent (Jackman and Smith 1943) A parallel with ulcerative colitis will be noted

A much rarer and more severe form is that in which the fistulous track burrows through the pelvic fascia apparently commencing in the pouch of Douglas and opens into the rectum above the sphincter or passes into the ischiorectal fossa or even into the vagina It is suggested that such a fistula may be due to proteolytic

a pathologic inflammatory process somewhere in the intestinal tract They do not occur in nervous gastrogenous pancreatic allergic or thyrogenic diarrhoeas There will be general agreement with this view

*Phase of physical signs*

The clinical characteristics and radiological features of established Crohn s disease are well known the significance of only certain of the leading signs and symptoms will therefore be discussed

*Diarrhoea* —This is the most constant symptom of the disease in all its stages though it may at first be slight and intermittent and is never as severe as in ulcera tive colitis Though severe bleeding may very occasionally occur blood is usually not to be observed in macroscopic quantities in the motions In the typical case fat digestion is not impaired If steatorrhoea is present it betokens extensive involvement of the intestine Cooke (1955) has found that the presence of steator rhoea before operation is associated with high post operative recurrence and mortality rates and surgical treatment in such cases is therefore strongly contra indicated

*Pain* —A characteristic feature of the pain in all phases of the disease is that it may precede the call to stool and may be relieved by defaecation Pain is usually situated in the region of the right iliac fossa or across the lower abdomen and only becomes severe and colicky in nature when the disease is sufficiently advanced to cause narrowing of the lumen of the ileum Low back pain may also be present It is important to realize that during the acute stages of the disease diffuse colicky pain does not necessarily demand surgical treatment as an urgent measure the narrowing of the lumen of the ileum which causes pain at this stage will probably be due to lymphatic oedema and not to fibrosis Complete rest at this time is likely to be accompanied by some degree of resolution so that the attacks become less insistent and the immediate danger is averted Colicky attacks over a lengthy period associated with visible peristalsis denote fibrosis and relief by operation will usually be indicated It should be noted that both nausea and vomiting are rare

*Anaemia* —A varying degree of anaemia is often though not necessarily present and may be down to a level of 70 per cent (Haldane) without there being any macro scopic evidence of blood loss In one of the author s patients the anaemia was megaloblastic in type and achlorhydria was present This patient had had a short circuit operation performed 5 years previously without affording relief Medical treatment failed to benefit the anaemia until excision of the diseased mass was performed This was followed by a partial recovery to the extent that the red cell count was maintained at about 4 million per cubic millimetre and the menses previously in abeyance became normal The patient eventually died at the age of 37 years 12 months after a radical excision of carcinoma at the cardia The total length of her medical history was 12 years

*The swelling* —The swelling is not always to be observed in the right iliac fossa but may be placed more centrally In one of the author s patients it was situated low in the left iliac fossa Occasionally it may lie wholly within the pelvis and its presence be revealed only by rectal or vaginal examination Repeated estimation of the size and character of the swelling is a very important guide to the progress of the disease

*Pyrexia* —During this phase the evening temperature may rise to 101 F and

continue so for weeks Occasionally it may reach an even higher level In one such case it pursued an unusual course suddenly falling to normal for no accountable reason at a time when a surgical procedure was contemplated

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*Pyrexia* —During this phase the evening temperature may rise to 101 F and

The ileum proximal to it may be a little distended there may be some evidence of spasm in the wall of the bowel on the other side of the ileo caecal valve and the normal angle of incidence between ileum and colon may be altered

The string deformity of Kantor is rarely if ever demonstrable before the stage of physical signs has been reached and the diagnosis obvious on clinical grounds At the same time it is a mistake to think that the presence of the string sign means that the bowel is already converted into a fibrous tube and that the activity of the disease has waned or wholly burnt out Such is very far from being the case for the radiological narrowing of the lumen is more than likely to be due to spasm and oedema and it may thus be at least partially reversible Indeed it is quite impossible to correlate this characteristic radiological appearance with any degree of permanent or irreversible change and its discovery is not necessarily to be regarded as an indication for early surgical intervention

The value of radiology in determining the degree of chronic obstruction and in the investigation of fistulas is recognized and well established

## Management

Though it is unwise to dogmatize upon the treatment of so unpredictable a disorder certain generalizations are permissible in the light of present day knowledge and experience Of particular importance is the study of the results—both short and long term—of radical extirpation and side tracking operations If the term recurrence is used in its very widest sense so as to include both failure to relieve major symptoms and the reappearance of symptoms after a period of temporary abeyance even without radiological or operative evidence of the return of the disease we must admit to a figure of at least 50 per cent within 5 years The figures from the Mayo Clinic (1954) show an incidence of 80 per cent after 15 years and Cooke (1955) of 78 per cent after 10 years Bockus (1954) estimates the 5 year recurrence rate after ample resection of the lesion to be between 50 and 70 per cent

The principal facts which emerge are first that surgical intervention should be avoided in the young subject during the florid active stages of the disease and secondly that if the progress of the disease is not stayed by medical measures and the employment of surgery is impelled while it is still active operation should be restricted to side tracking Any attempt at radical excision should be abjured One of the reasons for avoidance of even the side tracking operation while the disease is still active—a reason which has not been sufficiently emphasized—is that it is not always possible at this time to determine the exact limit of the disease by naked eye observation at operation and it is essential to success that transection of the ileum is made through healthy bowel Examination of frozen sections has been employed as a means of determining a healthy bowel level but the method is not infallible

Stated in general terms primary surgical treatment should be deferred until the disease has become quiescent or burnt out and should be restricted to the treatment of sequelae Until quite recent years most patients have undergone surgical exploration before the disease was suspected and a high proportion were submitted to appendicectomy If the abdomen is opened before the diagnosis has been made a lymphatic gland should be removed for microscopic and bacteriological investigation and the incision repaired with the utmost care There can be objection

*material escaping from a diseased loop of terminal ileum lying on the pelvic floor* (Crohn 1949)

*Perforation of the bowel* is a rare complication which may lead to the formation of a walled off abscess Severe haemorrhage from the inflamed intestine has been recorded

**Radiological examination**

Though symptoms usually precede any observable alteration of the outline or motility of the terminal ileum the latter may themselves precede the development



FIG 88 — *Tubular cast effect* Note unusual ileo caecal angle Diagnosis confirmed by mesenteric gland biopsy Eighteen months medical management The patient now has obstructive attacks and will probably need exclusion operation

of physical signs In other words the development of radiological changes is sandwiched somewhere between the phase of onset and the phase of physical signs

The early radiological abnormalities are those of spasm or of suggested swelling of the mucosa Such changes are not diagnostic of Crohn s disease and should be regarded as significant only if associated with a clinical history of Crohn s disease

The earliest definitive radiological change is the disappearance of the mucosal pattern of an area of terminal ileum so that it resembles a tubular cast (Fig 88)



FIG 89—Recurrence after exclusion ileo transverse colostomy Condition 4 years after operation upon a girl then aged 17 years with severe Crohn s disease with sinuses The disease has spread from the ileum across the anastomosis to involve the colon Hemicolectomy performed November 1952 Patient well except for micro cytic anaemia which re sponds well to iron (*Wallis Kendall*)



FIG 90—Spread of disease after non-exclu sion ileo transverse colostomy in a female aged 31 years Onset 15 years previously Figure illustrates spread of disease past the anastomosis 5 years after operation Hemi colectomy eventually performed

to diagnostic exploration when the nature of the disease is in doubt Under such circumstances the exploration should take the form of a small gridiron incision in the right iliac fossa undertaken with a minimum of disturbance

### Medical treatment

The essential component in medical treatment is rest The patient should remain in bed at home if need be until all physical evidence of activity disappears The diet should be high in calorie content and of low residue There is no specific remedy for the disease and antibiotics are of no proven value If the temptation to employ them is irresistible they should be used with discretion because they may be instrumental in initiating an enteritis (Zetzel 1956) Steroid compounds should also be used with caution during the active phase for fear that they may inhibit the normal response to inflammation perforation of the bowel has followed their use The main value of the steroid compounds seems to be in causing an improvement of appetite (and thereby nutrition) and in general well being

Progress is determined by diminution in symptoms and shrinkage of the tumour mass It is important not to regard the disease as having become burnt out until the haemoglobin and erythrocyte sedimentation rate become normal the weight is steady or increasing and the mass no longer tender Return to normal activities should not be permitted until these desiderata have been achieved

The patient despite recovery from the active process may experience occasional bouts of diarrhoea accompanied by colicky pain These are probably caused by intermittent obstruction and are an indication for the consideration of surgery

### Surgical treatment

The controversy between the exponents of radical excision and those of side tracking operations—all of whom have from time to time published unconvincing evidence in support of their allegiance—has largely subsided as a result of the realization that it is not so much on what is done as on when it is done that ultimate success depends If the disease progresses in spite of expert medical care or it becomes certain that medical measures are to fail then there can be no doubt whatsoever that a side tracking operation is to be preferred to excision It carries far less risk to life and at the worst it can do little harm Moreover it leaves the door open to the radical procedure if the side tracking operation is unsuccessful (Fig 89)

Apart from adopting surgery during the active phase of the disease the author prefers a side tracking operation in the young subject who has recovered from the florid type of the disease and radical excision in the older patient in whom the disease has run a quieter course

The presence of an external fistula will increase the hazard of resection particularly if multiple or combined with internal fistulas It will usually be expedient in such cases to limit the operation to an ileo colostomy Occasionally very gratifying results are obtained so that further surgical treatment is not needed Robinson (1953) has stressed the value of the conservative operation in the treatment of ileo vesical fistula though Williams (1954) is of the opinion that resection of the diseased intestine is preferred

**Other methods of treatment**

*Vagotomy*

Vagotomy has been advocated as a means of diminishing the intensity of diarrhoea thereby causing a general improvement in health sufficient to make further surgery justifiable at a later date but though some success in this connexion has been reported (Eddy 1951) it is not generally acceptable

*Radiotherapy*

Radiotherapy has been given an extended trial by Bargen (1954) and to a lesser extent by Keifer et al (1950) but it is very doubtful whether the dangers of the method do not exceed its benefits and it is probably unjustifiable except possibly for intractable operation failures

## RELATED CONDITIONS

The disease may spread upwards in continuity to involve the whole of the ileum the jejunum and even the duodenum and the stomach (Comfort et al 1950



FIG 91 —Chronic jejunitis in a boy aged 11 years (*By courtesy of Wilfred Sheldon and David Waterston*)

Martin and Carr 1953) or it may have a segmental distribution with considerable gaps in between

Widespread disease is likely to cause severe nutritional deficiencies (Cooke 1955) and in general surgery has no place in its treatment

The jejunum may however be affected over a limited segment or segments by the characteristic changes of Crohn s disease without there being any evidence of disease elsewhere in the alimentary tract

The symptoms of localized jejunitis appear to be mainly obstructive the disease is very rare (Fig 91) Surgical treatment if required should have a bias towards short circuit placed close to the obstruction rather than excision but it is very

*The operation*

The essential feature of the operative treatment is to transect the ileum so as to frustrate the tendency to extension of the disease proximally by direct spread Sections of the bowel must be through healthy intestine above the limit of disease and frozen sections may help to determine a healthy level if doubt exists

*Side tracking operation* —The cut end of the ileum should be implanted into the transverse colon as near to the hepatic flexure as convenient behind the great omentum Lateral ileo colostomy is very unreliable and in our experience gives at best only temporary relief In 4 patients in whom this operation had been performed excision became necessary in 3 after 4 years and in 1 after 5 years In one case there was radiological evidence of spread past the anastomosis which was confirmed at operation (Fig 90)

*Radical operation* —This can conveniently be performed through a transverse incision or through a previous midline scar after excision of the latter There is no need to increase the difficulty and risk of the operation by attempting to remove enlarged lymph nodes situated at a distance from the bowel Continuity should be restored by end to end anastomosis of the ileum to the distal cut end of the transverse colon

*Results of operation*

Tables in which operation cures are registered in figures carried to the right of the decimal point are not consistent with the behaviour of the disease In any event most recorded statistics date from the years during which surgery was regarded as the standard treatment

Figures purporting to show the relative value of ileo colic anastomosis and resection are open to criticism for they omit to compare the cure or respite rate of the two methods and deal only in terms of recurrence

The following figures of Garlock et al (1951) are the most frequently quoted as evidence that exclusion is a better operation than resection

| | |
|---|---|
| Exclusion ileo-colostomy | Recurrence 22 8 per cent<br>Mortality Nil per cent |
| Resection | Recurrence 46 per cent<br>Mortality 14 per cent |

On the other hand Marshall and Fecher (1954) believed that radical resection is the only method offering improvement or complete relief Their anticipated recurrence rate within 5–10 years is 30 per cent Armitage and Wilson (1950) and Armitage (1953) recorded the following experience

Of 34 patients treated for Crohn s disease 6 died after operation (2 after resection 2 after two stage resection 1 after laparotomy and 1 after short-circuit) One patient died later of other causes (two stage resection) Nine patients are untraced (3 after resection 2 after two stage resection 1 after short-circuit 1 after appendicectomy 1 after closure of fistula and 1 after short-circuit exclusion)

Of the remaining 18 patients 16 had had resections 1 a two stage resection and 1 a short-circuit There were 5 patients who had had no symptoms since operation (3 after resection 1 after two-stage resection and 1 after short-circuit) Nine patients had mild diarrhoea or a few attacks of severe diarrhoea (all resections) Four patients had symptoms suggestive of recurrence but barium meal follow through and enema examinations showed no lesion of the bowel (all resections) There were no proved recurrences



(a)



(b)

FIG 93 —Ligneous typhlitis in male aged 21 years Originally diagnosed as acute appendicitis and treated conservatively to allow the patient to sit examination There is some doubt as to whether appendicitis was primary or whether the appendix was involved secondarily to inflammation of the caecum which was woody hard Duration of illness up to time of resection was 12 months (a) Lipiodal radiograph showing sinuses following original laparotomy At one time provisional diagnosis was actinomycosis (b) Operation specimen probe passes through a sinus (c) Microphotograph showing thickened appendix buried in dense pericaecal fibrous tissue



(c)

important not to leave the patient with a permanent blind or partially blind loop of bowel

As with the jejunum the ascending transverse and distal colon may become affected by changes characteristic of Crohn s disease over a short segment

The disease may also spread downwards past the ileo caecal valve Usually this is over a very limited area of the caecum—a sympathetic reaction as it were to the troubles of its near neighbour Occasionally however the colon may be affected over a very wide area—even totally involved—and in such circumstances *the changes may not be in the least typical of Crohn s disease but identical with* those of ulcerative colitis The following is an example of this

A female aged 30 years was operated upon following history of abdominal symptoms extending over a period of 4 years Radiological and sigmoidoscopic examinations were negative Operation 22 9 52 Crohn s disease found and confirmed by lymph node biopsy Exclusion ileo transverse colostomy was performed Condition rapidly deteriorated after 1 month s respite Erythema nodosum and polyarthritis developed Cortisone therapy brought only temporary benefit Death occurred 9 3 53 At autopsy the whole mucosal surface of the large intestine was found to be affected by chronic ulcerative colitis with pseudo po yposis (Avery Jones )

It is well known that right sided colitis may leap the barrier of the ileo caecal valve which as Brooke (1953) has shown is often naturally incompetent or



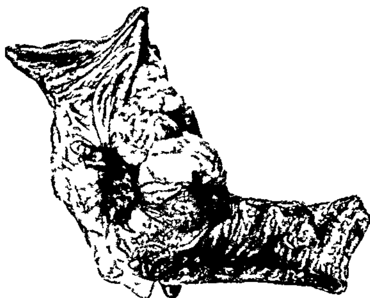
FIG 92 —Granuloma of the ascending colon in a female aged 58 years indistinguish able from cancer clinically and radiologically (*Wallis Kendall*)

becomes so as a result of the disease The ileum in such instances does not usually become converted into the thick walled rig d tube as in Crohn s disease and even if it eventually does so the primary change is mucosal and not submucosal

This reciprocal tendency for colon and ileum to infect or affect each other has been cited as evidence that Crohn s disease and ulcerative colitis are kindred disorders The kinship must however be a somewhat distant one for clinically and morphologically (Warren and Sommers 1954) the two diseases are distinct



(*a*)



(*b*)

FIG 95 —Chronic typhlitis associated with phthisis in female aged 30 years Bilateral upper lobar infiltration Sputum positive Sixteen months history of abdominal pain and sickness No diarrhoea Mass in right iliac fossa Bed rest 6 weeks with course of streptomycin and isoniazid (*Bruce Pearson*) Marked improvement in abdominal condition 22 1 54 Right hemicolectomy Patient now in excellent health (*a*) Radiograph showing narrowing of caecum and dilatation of ileum (*b*) Operation specimen Disease limited to caecum. (*c*) Section of lymph node (× 200) Complete investigation of pathological material failed to demonstrate tuberculosis (*H A Magnus*)



(a)



(b)

FIG 94 —Chronic typhlitis (a) Operation photograph Male aged 24 years with abdominal history indistinguishable from that of patients with phthisis and histology identical Complete investigation of operation material showed no evidence of tuberculosis (*H A Magnus*) (b) Section through mesenteric lymph node (× 200)

**Chronic typhlitis**

Changes in the wall of the caecum and contiguous ascending colon indistinguishable both on naked eye and microscopic examination from those characteristic of Crohn s disease have frequently been observed (Cotton 1955) Although

ligneous typhlitis have been suggested to describe it The inflamed appendix will be found lying embedded in peri caecal granulation tissue The condition may become complicated by sinus formation and may necessitate hemicolectomy (Fig 93)

*Primary chronic typhlitis*

The course of this disorder in the observed cases has been less acute than in typical Crohn s disease and diarrhoea is not a symptom Steady deterioration in health with progressive loss of weight and of appetite are characteristic features and malaena may rarely be noted (Fig 94)

One of the chief features of this form of chronic typhlitis is its association with pulmonary tuberculosis thus differing from Crohn s disease (Fig 95) It is extremely common in India where there is a sharp difference of opinion among those with great experience of the condition as to whether it is or is not tuberculous Mangalik and Misra (1952) of Lucknow believed that the condition is similar aetiologically to Crohn s disease whereas Anand (1956) of Amritsar claimed to have proved that the disease was tuberculous in 50 consecutive cases encountered during a period of 4 years Taylor (1954) believed that the fact that investigations for tuberculosis—including animal inoculation—are negative should not necessarily be accepted as an absolute criterion

It seems to follow that the borderline between demonstrable fibro caseous disease (now exceptionally rare in Great Britain) of the caecum and caecal granulomas showing only changes characteristic of Crohn s disease is a very shadowy affair—even indeed if it exists at all—and that at least some represent a reaction to a tuberculous process which escapes the more obvious clinical stigmas of chron c tuberculosis and which defies bacteriological identification

*Treatment*

In principle the optimum treatment of chronic typhlitis whether primary or secondary appears to be hem colectomy preferably in most cases following a period of rest and a course of streptomycin The results have been uniformly good In only one case has the condition been treated by us by exclusion ileo colostomy and in this case a fistula which followed appendicectomy persists

Radical treatment is also to be preferred when the disease is associated with pulmonary tuberculosis It goes without saying that for such patients the timing of operation demands especial attention and should be preceded and followed by anti tuberculosis care under the aegis of the physician

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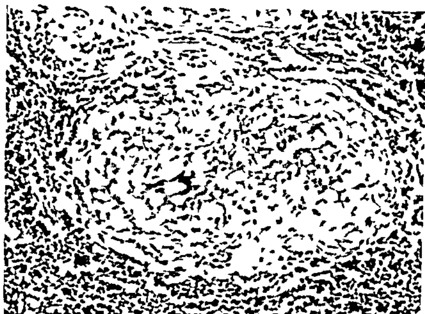


FIG 95 (c)

the condition often involves a limited area of ascending colon immediately above the caecum and sometimes is confined to the colon in this situation (Fig 92) it is convenient to label it typhlitis in order to avoid a clumsy title These changes may be secondary to the following (1) chronic inflammation of a solitary diverticu lum (2) solitary ulcer and (3) appendicitis

Identical changes may also be associated with pulmonary tuberculosis and finally may arise without any discernible local primary cause or other associated disorder In all these examples the lymph nodes will be found at operation to be enlarged (though not to a degree commensurate with that typical of the active phase of Crohn s disease) and to contain non caseating giant cell formations which are also present in the thickened rigid bowel wall These observations emphasize the fact that the presence of non caseating giant cell formations is not specific to Crohn s disease but is to be regarded as the normal reaction of the bowel and its lymph nodes to a noxious stimulus acting over a lengthy period of time

*Secondary chronic typhlitis*

Typhlitis secondary to chronic inflammation of a solitary diverticulum or to a solitary ulcer gives rise to a mass in the right iliac fossa which cannot readily be distinguished clinically or radiologically from carcinoma and the diagnosis may be revealed only after examination of an operation specimen Usually how ever the youth of the patient and the predominance of inflammatory signs can enable a clinical diagnosis to be made

*A rare form of chronic typhlitis is that due to appendicitis The wall of the cae* cum may become immensely thickened and so hard that the terms woody or

# CHAPTER 18

# THE DIAGNOSIS AND TREATMENT OF PROTOZOAL AND HELMINTHIC INTESTINAL INFECTIONS

W R M Drew

## PROTOZOAL INFECTIONS

### Intestinal Amoebiasis

**Diagnosis**

It is still not known what factors precipitate an attack of amoebiasis and the role of climate diet and changes in intestinal flora has not been fully investigated The types of amoebiasis encountered in different parts of the world are the familiar chronic form the sub-clinical case or carrier and acute amoebiasis Despite its variations the clinical picture in amoebiasis may easily be obscured by functional symptoms due to dysfunction of the large intestine Because of this wide clinical range the necessity for accurate diagnosis cannot be over emphasized Diagnosis will invariably depend on the laboratory finding of vegetative or cystic amoebae in the stools though the mere passage of *Entamoeba histolytica* does not mean that it is responsible for the patient s symptoms Indeed some races of *E histolytica* are considered to be relatively non pathogenic (Hoare 1950) The clinician may require special procedures such as sigmoidoscopic or radiological examinations to determine the extent of the intestinal lesions The laboratory worker requires experience in examining stools for *E histolytica* Direct examination of at least 6 fresh stool preparations is usually sufficient to confirm the diagnosis though concentration methods and special staining techniques may at times be in valuable *In vitro* culture of stools may occasionally assist in diagnosis Complement fixation tests still require further elaboration to make them reliable as a routine method of diagnosis

**Therapeutic considerations**

Development of the modern treatment of amoebiasis can be divided into two phases The first began with the introduction by Rogers (1912 a and b) of emetine for the treatment of intestinal and hepatic forms of the disease During this phase a number of other drugs with specific amoebicidal action were also brought into use The second phase was initiated by Hargreaves (1945) who first demonstrated the value of penicillin and succinyl sulphathiazole in the treatment of the secondary bacterial infection accompanying chronic amoebic dysentery Since then a number of other antibiotics with antibacterial or antiprotozoal activity have been used both singly and in combination with other agents for the treatment of this disease

*Some experimental evidence of activity of chemotherapeutic agents*

The *in vitro* cultivation of *E histolytica* was first carried out by Boeck and Drbohlav (1925) and later by Dobell and Laidlaw (1926) whose method of cultivation is still the best Dobell (1945) was successful in growing *E histolytica* in a fluid medium with one known strain of bacterium The presence of either bacteria bacterial products or rice

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# CHAPTER 18

# THE DIAGNOSIS AND TREATMENT OF PROTOZOAL AND HELMINTHIC INTESTINAL INFECTIONS

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They also found there was a four fold increase in the inhibition of these organisms when tetracycline or oxytetracycline were used with carbomycin

*Testing of amoebicidal substances in man* —It will be seen that the problem of the clinical evaluation of amoebiasis has been obscured by the fact that a number of drugs have been given on empirical grounds

In the therapeutic trials so far undertaken in man there has been a lack of uniformity Nearly all reports on the value of amoebicidal drugs take little account of the variation in the clinical types of the disease and make no distinction between patients passing vegetative forms and those with cysts in the stools It has been suggested by Adams and Maegraith (1953) that the time taken in the passage of the stools is the determinative factor concerned with which form appears in the stools This however may be an over simplification since some regard the appearance of the cystic form in the stools as reflecting a different stage of the disease In most of the clinical trials conclusions are drawn from small numbers of patients some of whom are out patients and therefore not under close supervision The follow up period is often far too short and in many studies no controls have been used A number of these investigations have been carried out in tropical countries where the possibility of re infection has not been taken into account

The reason why agents which are solely antibacterial are effective is not properly understood Once secondary bacterial infection is reduced or eliminated the body often appears to be capable of a successful recovery Thus since there is always this bacterial infection the combination of an amoebicidal drug and an anti bacterial drug is justified on theoretical grounds

**Chemotherapy of intestinal amoebiasis**

*Alkaloidal preparations*

*Emetine* —The alkaloid obtained from the dried root of *Cephoelis ipecacuanhae* is a complex isoquinoline which is administered by intramuscular injection and by mouth It dilates the coronary vessels and exerts a depressant action on cardiac muscle and on the conducting tissues of the heart Tachycardia lowering of blood pressure and electrocardiographic changes may result but these disappear in 1–2 weeks after cessation of treatment The electrocardiographic changes include prolongation of the P R interval and inversion of the T wave It exerts no effect on liver function The toxic effects produced are anorexia nausea abdominal pain diarrhoea dyspnoea precordial pain and polyneuritis

Emetine has a specific effect on vegetative forms of *E histolytica* but no effect on cysts The site of action is the tissues and not in the intestinal lumen Although the therapeutic and toxic ranges tend to overlap reports of the effects produced especially on heart muscle have in the past been grossly exaggerated Nevertheless preparations of emetine should be given carefully in appropriate dosage and with the patient resting in bed in hospital As a rough clinical guide to intolerance in the individual patient tachycardia a fall in blood pressure muscular weakness diarrhoea or abdominal cramps usually develop early Should these or electro cardiographic changes occur administration of the drug should be stopped The drug should not be given in the presence of heart or kidney disease in pregnancy or to very young children Preparations of emetine should never be given by injection and by mouth at one and the same time

flour is necessary in culture for the growth metabolism and multiplication of this amoeba and to keep it living for long periods For some reason which is not apparent the protozoon *Trypanosoma cru i* the causative organism of Chagas s disease has also been used as a growth factor The inability to grow the amoeba by itself has seriously hampered attempts to standardize methods of cultivation and testing of amoebicidal drugs

Of the drugs available emetine is amoebicidal in concentrations of 1 5 000 000 of medium fumagillin *in vitro* inhibits growth in a dilution of 1 130 000 000 of medium and the most recent addition dichloracet hydroxy methylanilide (Entamide) also possesses high activity *in vitro* All these substances possess amoebicidal rather than antibacterial properties On the other hand the halogenated oxyquinolines and the pentavalent arsenical compounds have little effect on *E histolytica in vitro*

*Experimental drug fastness* —The development of resistance to emetine and other drugs requires further confirmation although claims have been made to this effect Theoretically the development of drug fastness is possible but so far the number of strains investigated experimentally is small

Seneca and Murphy (1954) cultured 11 strains of *E histolytica* with oxytetracycline 1 strain of which became more resistant 2 strains of which became more sensitive while a further 8 showed no change After 10–20 sub cultures in the absence of oxytetra cycline the resistant strains maintained their resistance while sensitive strains returned to normal On the other hand Shaffer and Washington (1952) could not induce resis tance to emetine oxytetracycline or chlortetracycline after 38 consecutive serial cultures

*Animal experiments* —It might be thought that animal experiments would contribute much to the solution of the problem of testing amoebicidal drugs but the large number of variables and the fact that amoebiasis in most experimental animals does not conform to the pathology observed in man does not justify their use theoretically The macaque monkey does not show these disadvantages and it has been used to test new drugs for amoebicidal activity and to evaluate probable toxic effects in man

*Antibiotic combinations in vitro* —By means of *in vitro* experiments Seneca et al (1949) were able to show that penicillin and streptomycin inhibit the growth of a culture of *E histolytica* We now know that penicillin and streptomycin together are the equivalent of a broad spectrum antibiotic The work of Watt and Van de Grift (1950) (see Table I) proved synergism with two antibiotics of low amoebicidal activity

TABLE I

ANTIBIOTIC CONCENTRATIONS (MILLIGRAMS PER MILLILITRE) CAUSING INHIBITION OF ENTAMOEBA HISTOLYTICA

| *Drug* | *1st sub culture* | *4th sub culture* | *5th sub culture* | *6th sub culture* | *Remarks* |
|---|---|---|---|---|---|
| Polymixin D | 2 5 | 1 0 | 0 9 | 0 8 | Low amoebicidal effect |
| Circulin | 2 5 | | 1 0 | 0 9 | Low amoebicidal effect |
| Polymixin D + Circulin | 0 35 + 0 35 | 0 35 + 0 35 | | | Synergism |

*Conclusion*—Amoebicidal effect moderate

Anderson et al (1954) demonstrated some synergism *in vitro* neomycin and fumagillin inhibiting *E histolytica* only in the presence of a bacterial associate It appears that this synergism is brought about with the help of other bacteria in the gut Seneca and Bergendahl (1954) showed that there was a four fold increase in the inhibitory effect on different strains of *E histolytica* with equal amounts of tetracycline and oxytetracycline

*Synthetic halogenated compounds*

Since emetine is an isoquinoline derivative it is not surprising that a number of related halogenated compounds have shown amoebicidal activity

*Chiniofon*—When given by mouth Chiniofon is partly absorbed from the alimentary tract giving a peak blood level about 2 hours after administration Some is excreted in the urine but most of it is excreted in the faeces where it rejoins the unabsorbed part of the drug Chiniofon which contains about 27 per cent of iodine is iodo oxyquinoline sulphonic acid It is given by mouth in tablets of 0 25 gramme (3 75 grains) in a dosage of 1 tablet 3 times a day for 10-20 days preferably after meals As it is equally effective by mouth its use as a retention enema has generally been discontinued The drug is toxic to liver and kidneys and should never be given in the presence of disease of these organs Toxic effects are occasional symptoms of gastro intestinal irritation

*Diodoquin*—This is 5-7 diodo 8 hydroxyquinoline contains about 62 per cent of iodine and is supplied in tablets of 0 2 gramme (3 grains) The dose is 2-3 tablets 3 times a day after meals for 10 20 days As with Chiniofon only part of the drug is absorbed from the alimentary tract Toxic effects which are minimal are head ache nausea diarrhoea and pruritus ani It is the drug of choice for eradicating cysts especially in carriers In man it does not destroy the amoebae which have penetrated the intestinal wall

*Vioform*—This contains about 40 per cent of iodine and is iodo chlorhydroxy quinoline Each capsule contains 0 25 gramme (3 75 grains) and 3 capsules are given daily after meals for 10 days The toxic effects which are rare are nausea abdominal colic and diarrhoea The results of treatment are comparable to those of Diodoquin

These 3 drugs probably owe their curative action in part to inhibition of the bacterial infection and in part to cellular effects in the amoebae themselves

*Arsenical compounds*

Of the organic arsenical compounds the pentavalent members show definite amoebi cidal activity Nevertheless when given alone they do not cure amoebiasis but are useful additions to complete a course of treatment

*Carbarsone*—This contains about 29 per cent of arsenic and is 4-carbaminophenyl arsonic acid Each tablet contains 0 25 gramme (3 75 grains) 2 tablets are given daily for 10 days Toxic effects include occasional cutaneous reactions and since the drug is stored to a considerable extent in the liver and spleen its use is contra indicated in diseases of these organs and in hepatic amoebiasis

*Acetarsol and Treparsol*—Acetarsol (Stovarsol) dosage 0 25 gramme (3 75 grains) and Treparsol 0 25 gramme (3 75 grains) are less commonly used than Carbarsone Toxic effects may result from their absorption and the accumulation of arsenic in the body

*Milibis*—This is bismuth glycolyl arsanilate and is less effective than Carbarsone in the treatment of amoebiasis It is given as tablets (0 5 gramme 3 times a day for 7 days)

*Thiocarbarsone*—This is a trivalent compound containing about 19 per cent arsenic with an - SH group substituted for oxygen in part of the molecule The dosage is 0 1 gramme 3 times a day for 10 days It is said to be more effective and less toxic than the previously mentioned arsenical drugs This drug the effects of which are similar to those of Carbarsone is said to cure 90 per cent of patients

*Arsthinol* (Balarsen)—Most et al (1954) have shown that the drug is 88 per cent effective in children and adults both in active disease and in the carrier state using a

*Emetine hydrochloride* —This drug is given in a dosage of 0 06 gramme (1 grain) a day by intramuscular or deep subcutaneous injection Care should be taken to ensure that it does not accidentally enter a vein The daily dose for children is 1 milligram per kilogram of body weight The solution should be freshly prepared A course consists of not more than 12 injections and should not be repeated for at least 2 months

Most effective in acute amoebic dysentery or in acute exacerbations of chronic amoebic dysentery emetine hydrochloride relieves symptoms but is not usually enough to produce complete cure Emetine injections are more successful in hepatic than in intestinal amoebiasis The modern tendency in the treatment of the latter form is to give only 3 injections prior to treatment with emetine bismuth iodide by mouth

*Emetine bismuth iodide (E B I)* —This is a reddish powder insoluble in water given in gelatin capsules or enteric coated tablets which should be reasonably fresh The daily dose for adults is 0 06 gramme (1 grain) on the first day 0 12 gramme (2 grains) on the second day and 0 18 gramme (3 grains) on the third and the subsequent days the drug being given for a total of 12 days Vomiting is normally controlled by Avomine 25 milligrams thrice daily but may require a reduction in dosage Emetine bismuth iodide is best given on an empty stomach last thing at night with a sedative The dose for children should be proportionately smaller (1–2 milligrams per kilogram of body weight)

In hot humid climates the tablets readily deteriorate Freshly prepared capsules release a good concentration of the drug in the small intestine the stools becoming a dark grey colour The course of 12 days treatment is given to supplement emetine injections in acute intestinal amoebiasis or to replace them in the chronic form of the disease With this oral treatment the toxic effects of emetine are less likely to develop nevertheless the patient should be kept in bed and the pulse rate and blood pressure recorded daily any unusual change indicating the need for electro cardiographic examination In general it can be said that emetine bismuth iodide will cure well over 50 per cent of patients with intestinal amoebiasis and merely relieve symptoms and mask the disease in the remainder The drug should not be used for cyst carriers

The results of emetine bismuth iodide therapy show a general uniformity Dobell et al (1918) reported that 90 per cent of carriers were cured and Manson Bahr (1941) found a relapse rate of only 6 1 per cent after this treatment Recently Woodruff et al (1956) confirmed these results by finding a relapse rate of approxi mately 5 per cent in 220 patients treated with emetine bismuth iodide alone

From these results and from general clinical experience we know that emetine bismuth iodide is one of the most effective amoebicides However there is a group of refractory cases in which emetine bismuth iodide must be combined with anti bacterial therapy in order to eliminate the amoebic infection

*Conessine* —This is an alkaloid obtained from Indian Kurchi bark of *Holarrhena spp* and is given by mouth as the hydrochloride (dosage 1 5–7 5 grains a day) or as kurchi and bismuth iodide (5–10 grains a day for 14 days) It is said by certain French workers to achieve results similar and equal to those of emetine Owing to the severe toxic effects on the nervous system which may follow its use including the development of psychosis it is now considered that the drug should not be used

*Glaucarubin* —This substance isolated from the tropical American plant *Simaroube glauca* was found by Woodruff et al (1956) to give a relapse rate of 12 per cent in 66 patients passing vegetative or cystic amoebae in the stools The dosage used was 4 milligrams per kilogram of body weight No toxic effects were observed

*Bacitracin* —This antibiotic (a polypeptide) was used by Most et al (1950) in an average *oral* dosage of 80 000 units for 5–20 days with an over all cure rate of 66 per cent Similarly McHardy and Frye (1954) reported 31 2 per cent of failures in 205 patients In the dosage used the drug was practically non toxic though albuminuria and urinary casts may appear after 4 days possibly leading to tubular degeneration It is not absorbed from the alimentary tract Its use alone is not warranted but in combination with other drugs it may be useful

*Erythromycin* —Anderson et al (1954) reported a cure in 15 out of 17 patients Another series reported by Anderson et al (1955) showed that 12 per cent of children relapsed Further trials with erythromycin alone are indicated

*Entamide (dichloroacet hydroxy methylanilid)* —This was used by Woodruff et al (1956) to treat 45 patients with cysts or vegetative forms using a dosage of 12–21 milligrams per kilogram of body weight Of 17 patients given 12 milligrams per kilogram of body weight or more daily for 10 days 11 8 per cent relapsed There were no toxic effects on this dosage The advantage of this drug is that it is cheap but more extensive trials are indicated

At present the use of carbomycin anisomycin and neomycin alone is not justified by results Anisomycin shows marked toxicity

**Recommended drug treatment**

One can conclude from present evidence that the ideal combination in the treat ment of amoebiasis is most probably a specific amoebicidal agent combined with an antibiotic The need for using multiple drugs still exists The following courses are recommended

(1) *For acute symptoms with vegetative amoeba in the stools*

Days 1–5 —Injections of emetine hydrochloride (1 grain (0 06 gramme) daily) together with oral chlortetracycline (2 grammes initial dose 0 5 gramme six hourly)

Days 6–20 —E B I (first day 0 06 gramme second day 0 12 gramme and sub sequently 0 18 gramme daily)

Days 16–36 —Diodoquin (0 6 gramme 3 times daily)

(2) *For chronic attacks of dysentery with vegetative or cystic forms in the stools*

The same course of treatment omitting the initial injections of emetine hydro chloride

(3) *For the mild or symptomless patient with cysts in the stools*

Days 1–30 —Diodoquin (0 6 gramme 3 times daily) or carbarsone (0 25 gramme twice daily for 12 days)

**General treatment**

The patient should be nursed in a cheerful ward and encouraged to get well as quickly as possible Intercurrent disease and vitamin deficiency should be elimin ated The diet should be high protein high carbohydrate and may contain milk Vitamins such as the B complex should be given when necessary For anaemia iron may be required

*Post dysenteric symptoms*

After an attack of amoebic dysentery there may be intolerance of bulky fatty meals out pouring of mucus in the stools abdominal discomfort and fatiguability

dosage of 4–22 milligrams per kilogram of body weight for 5–7 days Both Thiocarbarsone and Arsthinol are well suited to large scale treatment of ambulant patients

**Antibiotic therapy**

Compared with conventional methods in general antibiotics by themselves are less efficient in the treatment of intestinal amoebiasis McHardy and Frye (1954) estimated that with synthetic drugs in the pre antibiotic period up to 1945 the recurrence rate was 7 per cent and they considered that treatment with a single antibiotic or synthetic drug is much less efficient than combined chemotherapy

One of the problems in the use of antibiotics alone or in combination is that strains of resistant bacteria especially staphylococci may develop This in turn makes appraisal of successful treatment more difficult

*The tetracyclines*

All the tetracycline drugs at present in general use are effective For intestinal amoebiasis they are given as follows

Two grammes initially then 2 grammes daily in divided doses as tablets or capsules for at least 1 week The total dosage should be in the region of 20 grammes They act locally in the large intestine as only part of the oral dose is absorbed Toxic effects which with this dosage are not common are nausea vomiting diarrhoea and pruritus ani There is always a danger of producing super infection with fungi coliforms or resistant staphylococci

*Chlortetracycline (Aureomycin)* —Woodruff et al (1956) found that a course of this drug failed to clear 3 out of 6 patients of *E histolytica* cysts present in the stools These results are dissimilar to those of McVay et al (1949) in which the drug eliminated *E histolytica* in 33 out of 37 patients and McHardy and Frye (1954) with 16 6 per cent of failures in the treatment of 697 cases

*Oxytetracycline (Terramycin)* —This according to reports of trials conducted especially in the United States of America is one of the most valuable drugs in the treatment of amoebiasis Most et al (1950) found it 100 per cent effective using a dose of 2 grammes a day in 200 patients who were followed up for a periods of 6 months Among other reports of its effectiveness is that of McHardy and Frye (1954) with 8 5 per cent of failures in 435 cases Woodruff et al (1956) found that 2 patients relapsed out of 14 having been given a course of this antibiotic

*Tetracycline (Achromycin)* —This antibiotic has an effect similar to oxytetracycline Seneca (1955) reported 19 patients cured out of 20 who were given 1 5 grammes daily for 8 days This antibiotic still requires further trials to confirm its efficiency in amoebiasis

*Other antibiotics*

*Fumagillin* —This has been the subject of much research and is favoured by McHardy and Frye (1954) who found a 14 per cent rate of relapse in acute amoebic dysentery in 119 patients They concluded that no one drug is always successful or a complete amoebicide Woodruff et al (1956) treated 32 patients with 60 milligrams of fumagillin a day and a further 2 cases with 30 milligrams a day In 26 cases the treatment lasted for 14 days and in the remainder for 8 days All except 7 of the 34 patients were followed up The toxic ill-effects included skin reactions nephritis and gastric irritation Only 1 relapse occurred out of the 27 patients who were followed up Anderson et al (1955) reported a recurrence rate in 43 per cent of children treated with fumagillin

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*Tetracycline (Achromycin)*—This antibiotic has an effect similar to oxytetracycline Seneca (1955) reported 19 patients cured out of 20 who were given 1 5 grammes daily for 8 days This antibiotic still requires further trials to confirm its efficiency in amoebiasis

*Other antibiotics*

*Fumagillin*—This has been the subject of much research and is favoured by McHardy and Frye (1954) who found a 14 per cent rate of relapse in acute amoebic dysentery in 119 patients They concluded that no one drug is always successful or a complete amoebicide Woodruff et al (1956) treated 32 patients with 60 milligrams of fumagillin a day and a further 2 cases with 30 milligrams a day In 26 cases the treatment lasted for 14 days and in the remainder for 8 days All except 7 of the 34 patients were followed up The toxic ill-effects included skin reactions nephritis and gastric irritation Only 1 relapse occurred out of the 27 patients who were followed up Anderson et al (1955) reported a recurrence rate in 43 per cent of children treated with fumagillin

*Glaucarubin*—This substance isolated from the tropical American plant *Simaroube glauca* was found by Woodruff et al (1956) to give a relapse rate of 12 per cent in 66 patients passing vegetative or cystic amoebae in the stools The dosage used was 4 milligrams per kilogram of body weight No toxic effects were observed

*Bacitracin*—This antibiotic (a polypeptide) was used by Most et al (1950) in an average *oral* dosage of 80 000 units for 5–20 days with an over all cure rate of 66 per cent Similarly McHardy and Frye (1954) reported 31 2 per cent of failures in 205 patients In the dosage used the drug was practically non toxic though albuminuria and urinary casts may appear after 4 days possibly leading to tubular degeneration It is not absorbed from the alimentary tract Its use alone is not warranted but in combination with other drugs it may be useful

*Erythromycin*—Anderson et al (1954) reported a cure in 15 out of 17 patients Another series reported by Anderson et al (1955) showed that 12 per cent of children relapsed Further trials with erythromycin alone are indicated

*Entamide (dichloroacet hydroxy methylanilide)*—This was used by Woodruff et al (1956) to treat 45 patients with cysts or vegetative forms using a dosage of 12–21 milligrams per kilogram of body weight Of 17 patients given 12 milligrams per kilogram of body weight or more daily for 10 days 11 8 per cent relapsed There were no toxic effects on this dosage The advantage of this drug is that it is cheap but more extensive trials are indicated

At present the use of carbomycin anisomycin and neomycin alone is not justified by results Anisomycin shows marked toxicity

## Recommended drug treatment

One can conclude from present evidence that the ideal combination in the treatment of amoebiasis is most probably a specific amoebicidal agent combined with an antibiotic The need for using multiple drugs still exists The following courses are recommended

(1) *For acute symptoms with vegetative amoeba in the stools*

Days 1–5—Injections of emetine hydrochloride (1 grain (0 06 gramme) daily) together with oral chlortetracycline (2 grammes initial dose 0 5 gramme six hourly)

Days 6–20—E B I (first day 0 06 gramme second day 0 12 gramme and subsequently 0 18 gramme daily)

Days 16–36—Diodoquin (0 6 gramme 3 times daily)

(2) *For chronic attacks of dysentery with vegetative or cystic forms in the stools*

The same course of treatment omitting the initial injections of emetine hydrochloride

(3) *For the mild or symptomless patient with cysts in the stools*

Days 1–30—Diodoquin (0 6 gramme 3 times daily) or carbarsone (0 25 gramme twice daily for 12 days)

## General treatment

The patient should be nursed in a cheerful ward and encouraged to get well as quickly as possible Intercurrent disease and vitamin deficiency should be eliminated The diet should be high protein high carbohydrate and may contain milk Vitamins such as the B complex should be given when necessary For anaemia iron may be required

### *Post dysenteric symptoms*

After an attack of amoebic dysentery there may be intolerance of bulky fatty meals out pouring of mucus in the stools abdominal discomfort and fatiguability

These symptoms clear up after months or years Following treatment the criteria of cure should as far as possible be standardized and include examination of at least 6 specimens of stools sigmoidoscopy and if necessary a barium enema

### *Hepatic Amoebiasis*

Metastatic involvement specially of the liver may occur months or years after an attack of intestinal amoebiasis This may be difficult to diagnose especially when there is no evidence of the original intestinal infection

The miliary areas of necrosis coalesce or grow larger forming one or more abscesses In these the vegetative amoebae flourish without secondary bacterial infection which is present in only a small percentage of such cases

When the lesion is in the upper part of the right liver lobe symptoms are associated with signs of congestion collapse or effusion at the right base When the abscess is in the lower part of the right lobe the symptoms and signs are predominantly abdominal If the left lobe of the liver is affected swelling in the epigastrium may be found

Repeated stool examination reveals the presence of *E histolytica* in not more than 50 per cent of such patients Besides an increased total leucocyte count a raised sedimentation rate is suggestive of liver involvement Radiological evidence of a localized bulging or raised right diaphragm showing limited or paradoxical movements provides confirmatory evidence of this complication A small pleural effusion may be present The finding of typical amoebic pus on exploratory puncture may be necessary to confirm the diagnosis More often the use of emetine or chloroquine may be required as a therapeutic test The use of these drugs may be life saving but an enlarged liver in the tropics does not necessarily imply amoebiasis The complement fixation test may be useful in obscure cases

Most patients with pulmonary amoebiasis show lesions which have spread from the right lobe of the liver but on rare occasions localized or diffuse shadows which disappear with treatment are seen radiologically in other parts of the lung fields Other remote sites like the brain are of extremely unusual occurrence Very rarely dermal amoebiasis results from localized spread around an abdominal wound a colostomy opening haemorrhoids or an anal fissure

## General management and drug therapy

*Emetine hydrochloride*

General treatment includes suitable diet warmth and rest in bed especially when emetine is being given Of the drugs available emetine hydrochloride is still preferred The dose is 1 grain daily for 10–12 days administered by intramuscular or deep subcutaneous injection

*Chloroquine*

The anti malarial drugs chloroquine diphosphate (Aralen) and chloroquine disulphate (Nivaquine) both quinoline derivatives are extremely effective in hepatic amoebiasis because they are concentrated 500–600 times in the liver Conan (1948) carried out the first clinical trial Murgatroyd and Kent (1948) demonstrated the effectiveness of chloroquine in a patient with a sinus leading to a liver abscess

*E histolytica* disappeared from the discharging pus and the sinus healed by the twelfth day Recent experience confirms these findings

*Recommended drug treatment*

Days 1– 2 Chloroquine (0 3 gramme (base) three times daily)
Days 3–21 Chloroquine (0 15 gramme (base) three times daily)
Days 12 21 Injections of emetine hydrochloride (0 06 gramme) daily
Days 22–42 Diodoquin (0 6 gramme three times daily) to clear up any associated intestinal infection

*Antibiotics*—When secondary bacterial infection is present either penicillin with streptomycin one of the tetracyclines or erythromycin stearate may also be required This last named drug is concentrated in the liver 3–4 times more than in other parts of the body Anderson et al (1955) reported successes in hepatic amoebiasis with erythromycin stearate alone in 28 out of 36 cases and Nelson et al (1955) had only 8 failures in 28 patients treated with this antibiotic

**Operative treatment**

When operative treatment is indicated—for example when a large abscess is present or there has been failure to respond to chemotherapy alone—emetine hydrochloride or chloroquine cover must first be given The use of exploratory puncture with a large bore needle inserted on the right side into the point of maximum tenderness or into the seventh or eighth intercostal space is preferable to open or closed drainage which however is always necessary when a transperitoneal approach is required to drain the abscess

**Criteria of cure**

Absence of symptoms the return of the liver to normal size with disappearance of tenderness and a normal erythrocyte sedimentation rate indicate that the amoebic infection is no longer active As with intestinal infection the tendency to latency and relapse is present in hepatic amoebiasis It is generally agreed that all cases should have a course of treatment for intestinal amoebiasis whether or not there is evidence of infection of the colon

## GIARDIASIS

*Giardia intestinalis* a common flagellate of man and animals lives in the small intestine and may be found associated with amoebiasis It is considered capable of causing mechanical irritation and interfering with the absorption of fats diarrhoea and cholecystitis occur in some patients Nevertheless the aetiological relationship of *Giardia* to these conditions is still lacking Diagnosis is made by the finding of this flagellate (or its cystic form) in the stools

**Treatment**

Mepacrine hydrochloride (Atebrin Quinacrine) in a dosage of 0 1 gramme three times daily is specific for this infection and eliminates it from the stools in 3–5 days Nevertheless it has been observed that symptoms may continue following this treatment

## HELMINTHIC INFECTIONS

### Cestodes

**Taeniasis**

*Taenia saginata* is not uncommonly encountered in the United Kingdom The worm can inhabit the alimentary tract without producing symptoms on the other hand it may produce digestive disturbance diarrhoea and loss of weight anaemia and eosinophilia may be present The diagnosis is made by the identification of segments in the patient s stools

*Treatment*

Treatment with either filix mas or mepacrine is satisfactory

*Filix mas*—The following routine recommended by Asher (1953) produces good results *On admission to hospital the patient is given a liquid diet for 3 days Mist alba* ½ ounce is given each morning and mist cascara ½ ounce each night On the fourth day nothing is given by mouth except the following

- 7 a m — 1 ounce mist alba
- 8 a m — Extractum filicis (10 minims) in a capsule repeated at 15 minute intervals until a total of 8 doses has been administered
- 11 30 a m — A warm saline enema is given and the head of the tape worm is usually passed
- 12 30 p m — Another enema is administered if the head of the worm has not been passed

All stools must be kept until the head has been found and identified

The above regime must be modified for children A semi solid low fat diet is given during the first 3 days and purgatives reduced according to age The total number of doses should be reduced from 8 to 2 and both doses of filix mas should be 1 minim per year of age

Toxic symptoms include nausea vomiting colic cramps yellow vision temporary blindness jaundice convulsions and albuminuria

The drug should not be administered in the presence of cardiac hepatic or renal disease Permanent blindness and death have been reported but with the recommended doses the above procedure is safe

*Mepacrine hydrochloride* (*Atebrin Quinacrine*)—After starvation a single dose of 1 gramme mepacrine hydrochloride followed 2 hours later by a saline purge is effective The routine recommended by Sodeman and Jung (1952) gives good results On the day before treatment only a milk diet with a large dose of castor oil or magnesium sulphate is administered On the next morning a saline enema is *followed 1 hour later by 0 6 0 8* gramme *of mepacrine hydrochloride two 0 1* gramme tablets being given each 5 minutes together with 0 6 gramme of sodium bicarbonate in a little water A large dose of magnesium sulphate is given 2–4 hours later and food is withheld until the bowels have moved The appearance *of the head may be delayed for some days Mepacrine is not recommended for* children under the age of 8 years The toxic symptoms are nausea vomiting and rarely some mental disorientation

*Taenia solium (pork tape worm)*

The distribution of *T solium* is world wide though in Great Britain it is now rarely encountered Diagnosis depends on finding segments of the worm in the

faeces The importance of this worm is that man may act as an intermediate host with cystic larvae being secondary throughout the muscles and brain and giving rise to somatic cysticercosis The presence of cysticercosis is confirmed radio logically by the appearance of calcified cysts in voluntary muscles and occasionally in the white matter of the brain

Treatment for intestinal infestation with the tape worm is the same as for *T solium* There is no satisfactory treatment for cysticercosis The main symptom epilepsy should be treated along the usual lines

*Diphyllobothrium latum (fish tape worm)*

This parasite is very rare in Great Britain The clinical symptoms are similar to those of *T saginata* but occasionally adequate absorption of vitamin $B_1$ is pre vented and macrocytic anaemia may result Treatment for this intestinal infestation is the same as described for *T saginata* In the presence of macrocytic anaemia vitamin $B_1$ should be given for some weeks

*Echinococcus granulosus (dog tape worm)*

This small tape worm is found in countries where man lives in close contact with dogs and sheep The adult worm does not affect man but the cystic larvae deposited in tissues cause hydatid disease The cysts may give rise to symptoms may rupture or become secondarily infected Liver lungs and occasionally bones brain or kidneys are effected

There is no medical treatment for hydatid disease Penicillin is indicated for secondary infection Aspiration should not be attempted in view of the danger of dissemination Complete surgical removal is indicated if practicable but only in the presence of severe symptoms There is a real danger of spreading the infection at operation and in many cases the best solution to this problem is marsupializa tion by stitching to the abdominal wall thus allowing the cysts to drain externally and finally heal by granulation The wound should be washed out with weak formalin

NEMATODES

**Ancylostomiasis (hook worm)**

*Ancylostoma duodenale* and *Necator americanus* have a wide distribution especially in the tropics In Europe this infestation is found in southern countries especially Italy and in persons returning from abroad It causes few if any symptoms in healthy adults on a good mixed diet It can however be a serious chronic disease characterized by chronic blood loss often resulting in severe anaemia diarrhoea abdominal pain flatulence and general debility

Oedema is frequently associated with severe infestation and death from anaemia is not uncommon in children The microcytic anaemia and eosinophilia will draw attention to the need for microscopic examination of the stools when the characteristic eggs will be found

When the anaemia is of a severe grade toxic anti helminthic drugs should be avoided until the patient s anaemia has been adequately treated Carbon tetra chloride has now been replaced by tetrachlorethylene which is the treatment of choice

*Treatment*

*Tetrachlorethylene*—For two days prior to therapy the patient should receive a light fat free diet and avoid alcohol A saline purge (adults sodium sulphate 1–2 ounces) is then given at night and the tetrachlorethylene taken on an empty stomach the following morning On the day of treatment the patient must remain in bed receive a further saline purge 2 hours after taking the drug and have no food until the bowels have been well opened

The adult dose of tetrachlorethylene is 4 millilitres (0 2 millilitre per year of age for children) It is swallowed in capsules Except in the presence of alcohol or fats absorption is very slight and toxic effects are limited to transient headache and vertigo

*Oil of chenopodium*—This may be combined with tetrachlorethylene but it is much more toxic and may cause headache dizziness blurring of vision paraesthesiae circulatory collapse and kidney or liver damage The above routine is carried out but gelatin capsules containing 2 7 millilitres of tetrachlorethylene with 0 3 millilitre of oil of chenopodium are used instead of the tetrachlorethylene by itself Oil of chenopodium is contra indicated in cardiac renal or hepatic disease peptic ulceration pregnancy and childhood Its use should be confined to treating patients who have relapsed after initial therapy with tetrachlorethylene alone when the combined treatment may be given after one week

*Hexylresorcinol*—This is only moderately effective against hook worms and should be given in mixed infestations with *Ascaris lumbricoides* before tetrachlorethylene is employed as the latter drug tends to encourage the formation of obstructive boli of round worms Details of treatment are described below Occasionally in very severely anaemic patients blood transfusion should be given before anti helminthic therapy is started

The stools should be re-examined for ova at the fourth and twelfth weeks after treatment

## Ascariasis (round worm)

*Ascaris lumbricoides* the round worm a common parasite in childhood usually causes few symptoms It is found in all parts of the world Larvae in the circulation or lungs may cause fever urticaria eosinophilia haemoptysis or eosinophil pneumonia The symptoms due to the presence of adult intestinal worms are colic vomiting disturbances of appetite and occasionally appendicitis or obstruction Diagnosis is made by identification of worms or eggs in the faeces or by the presence of larvae in the sputum

*Treatment*

*Hexylresorcinol*—This drug is the treatment of choice for adults It is administered in gelatin-coated capsules each containing 0 2 gramme The dose for adults is 1 gramme (children aged 9–11 years 0 6 gramme those between 12 and 14 years 0 8 gramme) given on an empty stomach A saline purge on the previous evening is advisable but sodium sulphate (16 grammes) should be given 2 hours after treatment and fasting should be continued for another 2–3 hours

The drug is relatively non toxic Some gastro intestinal irritation may follow and if the capsules are chewed ulceration of the buccal mucous membrane may occur This makes it unsuitable for young children for whom piperazine citrate is preferable Patients may remain ambulatory during therapy which should be repeated in 4 days if the best results are to be obtained

*Piperazine salts*—These substances are non toxic are not absorbed to any extent and have a wide margin of safety They possess marked activity in ascariasis

*Piperazine citrate* may be given as a syrup (500 milligrams per drachm) The quantity for an adult is a single dose of 3 grammes just before the evening meal it may also be given as tablets No starvation or purgation is necessary Other salts such as the tartrate adipate and hydrate are also used The dose for children is given below

*Diethylcarbama ine* (Banocide Hetrazan) —This is more toxic than piperazine citrate Its use in ascariasis is liable to cause toxic effects such as headache vertigo vomiting and allergic skin reactions Anti histamine drugs may be used to lessen these side-effects Santonin is considerably less effective and more toxic than the above remedies

Ascaris pneumonia should be treated symptomatically It is wise to give an anti biotic in view of the likelihood of secondary bacterial infection

## Strongyloidiasis

This rare infection caused by *Strongyloides stercoralis* was seen in prisoners from the Far East after World War II Auto infection is believed to occur because the infection has been reported to persist for more than 20 years Diagnosis is made by finding the characteristic larvae on stool examination At present there is no effec tive treatment though Anthiomaline by injection and gentian violet by mouth have been used without much success

## Enterobiasis

*Enterobius vermicularis* is the commonest of worms found in European children The main symptom pruritus ani which may be intolerable and give rise to scratch ing is most important because of auto infection Heavy infections in children may be associated with anorexia and colic The diagnosis can be confirmed by identifying eggs in swabbings or scrapings from the peri anal skin

### Treatment

*Piperazine citrate* — White and Standen (1953) found this compound to be most efficient in the treatment of enterobiasis A dose of 50–75 milligrams per kilogram of body weight daily for 7 days and the course repeated after a rest period of 7 days Neither starvation nor purgation is necessary The piperazine citrate is made up as a pleasant tasting syrup (Antepar Elixir) so that the treatment is especially suitable for children

*Oxytetracycline* (Terramycin) —This antibiotic is also very effective A single dose of 2 grammes (1 5 grammes in children aged 5–10 years 1 gramme in children under the age of 5 years) is given for 7 consecutive days it may cause gastro intestinal irritation

An anti histamine cream should be applied if excoriated lesions are present in the anal area

It is essential to do everything possible to discourage anal scratching the fingernails should be cut short and scrubbed conscientiously before meals cotton gloves should be worn at night Hexylresorcinol Diphenan gentian violet capsules or quassia enemas are no longer indicated

## Trichiniasis

*Trichinella spiralis* a small nematode parasite of the rat and pig is occasionally conveyed to man by eating infected pork and is usually confined to damp climates Within 24 hours of infestation diarrhoea and vomiting may occur The symptoms of peri orbital oedema intense muscular pains pyrexia eosinophilia and occasionally myocarditis and meningitis appear after about 10 days

*Treatment*

If the diagnosis is suspected in the gastro intestinal stage tetrachlorethylene should be given at once in the dosage recommended for hook worm and followed by a saline purge Once symptoms of tissue infection have occurred little effect is likely to follow anthelmintic measures Recently on the assumption that an antigen antibody reaction was an important factor in producing these symptoms ACTH has been given with encouraging results and it appears that this drug (or cortisone) in normal full doses is well worthy of a trial

Chemotherapy has not been encouraging

## TREMATODES

### Schistosomiasis

This chronic disease is rarely diagnosed before the infection has become localized in the large intestine (or bladder) by which time ova will be found on stool or urine examination Sigmoidoscopy may reveal the presence of chronic ulceration of the colon with or without polypi and rectal biopsy may reveal the presence of charac teristic tubercles containing ova Eosinophilia is marked and complement fixation and intradermal tests are usually positive

*Treatment*

*Lucanthone hydrochloride* (*Nilodin Miracil D*) —This drug was developed by the Germans during World War II and is one of the most active thioxanthone com pounds It is given by mouth in tablet form and can produce such ill effects as gastro intestinal irritation insomnia and reddish brown discoloration to the palms and soles The drug can be extracted from the urine which is yellow The daily adult dose is 1–2 grammes in divided doses for 3–5 days Anorexia nausea and vomiting are usually controlled by the administration of 1 grain of pheno barbitone (60 milligrams) twice daily and only occasionally necessitate a reduction in dosage In intestinal schistosomiasis (usually *Schistosoma mansoni* or *S japonicum*) it is less effective than in the urinary form of the disease symptoms being alleviated with a low rate of cure

*Potassium or sodium antimony tartrate* —When given intravenously these are still the most effective drugs in intestinal schistosomiasis The sodium is less toxic than the potassium salt but both are tissue irritants Toxic effects are vomiting salivation a metallic taste cough and bradycardia The injection should be given slowly on an empty stomach They are cardiac depressants and severe hypotension may follow so that the patient should lie down for the injection Occasionally exfoliative dermatitis may occur which is an indication for BAL therapy A course of antimony tartrate consists of 12 injections totalling 1 8 grammes (30 grains) The initial adult dose is 30 milligrams (½ grain) the second 60 milligrams (1 grain) the third 90 milligrams (1½ grains) and subsequently 120 milligrams (2 grains) may be given (The full dose for children is 2 milligrams per kilogram of body weight ) Reactions necessitate reduction in dosage and longer spacing of injections

Two other trivalent antimony preparations sodium antimony gluconate (Triostam) given intravenously and antimony lithium thiomalate (Anthiomaline) given intramuscularly are rather less effective than the foregoing antimony preparations

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which may be designated as rectal and rectosigmoid or left colon in type are actually examples of superficial involvement of the entire colon

**The ordinary distal type**

A common variety the ordinary distal type is characterized by involvement of the rectum usually with extension proximally for a variable distance to involve contiguous parts of the colon not rarely the entire colon Ninety three per cent of 2 000 cases reviewed by Sloan et al (1953) were so labelled Eighty five per cent of 182 cases in the Graduate Hospital material belonged in this category (Table II)

TABLE I

ANATOMICAL TYPES—TOPOGRAPHICAL LOCALIZATION

| *O d nary distal (rectum always)* | *Regional or segmental (rectum never)* | *Enterocolitis* |
|---|---|---|
| Rectum or rectum and sigmoid | Continuous involvement | Continuous involvement ileum and part of colon |
| Left colon | Skip areas | Skip areas in small intestine colon or both |
| Whole colon (occasional back wash) | | |

TABLE II

TOPOGRAPHICAL DISTRIBUTION —
182 CASES

| | *No of ca es* | *Percentage* |
|---|---|---|
| Rectum | | |
| rectum and sigmoid | 27 | 14 8 |
| Left colon | 39 | 21 4 |
| Entire colon | 88 | 48 4 |
| Regional (segmental) | 11 | 6 1 |
| *Enterocolitis* | 17 | 9 5 |

S f d se at t whe fi t se t G d t H p t l

*Rectum or rectum and sigmoid (R RS)*

This sub group ordinarily comprises a large number of patients with ulcerative colitis who are ambulatory and who may never require hospitalization or at least not until late in the course of the disease Most often the illness is afebrile diarrhoea not too severe and bleeding only slight Commonly attacks tend to be self limited (4–16 weeks) In some instances a course characterized by mild recurrences every 6–24 months may continue for years or even throughout life However a more severe or even an acute fulminating relapse may occur at any time Obviously not many of these very mild cases are included in this hospital series A review of office or out patient records would reveal a great number of these mild cases with involvement confined to the rectum or rectum and sigmoid

In the hospital series only 14 8 per cent of cases had involvement confined to the rectum or rectum and sigmoid (Table II) Approximately 80 per cent of

# CHAPTER 19

# ULCERATIVE COLITIS

## I CLASSIFICATION OF TYPES CLINICAL BEHAVIOUR LIFE HISTORY PROGNOSIS

H L BOCKUS J L A ROTH E BUCHMAN AND M KALSER

THIS chapter deals with clinical behaviour patterns in so called non specific ulcerative colitis *We have drawn freely upon the statistical analysis of case* records (1927–53) from the Gastroenterologic Service Graduate Hospital University of Pennsylvania presented at the International Congress of Gastro enterology London July 18–21 (Bockus et al 1956)

*Percentages given in relation to classification* of types are derived from an analysis of 182 well documented cases figures quoted in relation to clinical behaviour and prognosis refer to the analyses of 125 case records of patients followed for more than 3 years In the latter group the duration of disease prior to our first study was from 3 weeks to 35 years averaging 5 years The duration of follow up (personal) subsequent to our initial studies was from 3 to 25 years averag ing 6 years It must be realized that percentages given here which deal with clinical behaviour patterns need for operation and prognosis do not represent a fair cross section of the clinical behaviour or severity of ulcerative colitis as it is seen throughout the United States of America In the Graduate Hospital series the disease was usually far advanced However it is likely that our clinical material may be compared fairly with that of other metropolitan teaching hospitals in the north eastern and north central parts of the United States of America

For many years it has been our practice to attempt to classify cases of ulcerative colitis according to certain topographical and clinical types It has seemed possible that the clinical behaviour life history and prognosis of the disease may to some extent be influenced by the specific anatomical type or clinical variety or both at the time of onset Obviously many features are common to all varieties and eventually in many instances the terminal stages may be the same

## ANATOMICAL TYPES—TOPOGRAPHICAL LOCALIZATION

The anatomical or topographical classification is given in *Table I Any attempt at* classification based on the initial site of involvement presents some difficulty In many patients the disease process may have spread beyond the initial site of in volvement prior to the time of an original classification A designation of type if made by the clinician must be based upon sigmoidoscopy and radiology One can be relatively certain concerning the presence or absence of disease of the rectum and low sigmoid since active inflammation in that area is easily visualized through the sigmoidoscope However superficial mucosal changes at higher levels in the colon may fail to give rise to definitive radiological signs It is difficult to know how often radiological findings are negative or equivocal when the inflammation is superficial but nevertheless definite Consequently it is likely that some cases

ulcerative colitis in association with chronic inflammation of some part of the small intestine usually the ileum and which is pathologically identical with non specific regional enteritis

In other instances when true ulcerative colitis is associated with some inflammatory changes in the terminal inches of the ileum but the ileal involvement lacks the striking granulomatous stenosing lymphogenous character of the true non specific enteritis the designation ordinary ulcerative colitis with back wash may be employed We agree with the opinion expressed by Warren et al (1954) that this latter type of ileal involvement accompanying ordinary chronic ulcerative colitis can usually be differentiated from the ileal lesion of primary enteritis Unfortunately there seems to be no pathological difference in the character of the colonic lesion whether it be pure ulcerative colitis or the colitis accompanying some instances of regional enteritis here designated as enterocolitis It is important to keep in mind that in true enterocolitis the ulcerative involvement of the colon seldom extends into the rectum or low sigmoid whereas in so called back wash ileitis the rectum indeed the entire colon is almost always involved The sub varieties of enterocolitis are listed in Table I

We have been rather surprised to note the high incidence of involvement of the ileum in ordinary ulcerative colitis reported in the literature for example 28 per cent of 103 cases reported from the Mayo Clin c by McCready et al (1949) It was mentioned that the type of pathology of the ileum in these cases resembled more the morphological character of ulcerative colitis than that of regional enteritis For this reason it is assumed that many of the cases reported by McCready and his colleagues were probably instances of chronic ulcerative colitis with so called back wash

In our material there were only 4 instances with radiological evidence of striking back wash in the series of 61 patients with involvement of the entire colon (6 6 per cent) This designation of back wash ileitis distinguished from true enterocolitis has clinical importance since one rarely if ever sees a recurrence of ileitis after colectomy performed for ordinary ulcerative colitis with or without back wash whereas the recurrence rate after operation for true enterocolitis in our patients is in the neighbourhood of 50 per cent within 5 years There are 17 instances of true enterocolitis in our entire group of 182 cases or 9 5 per cent (Table II)

**Longitudinal spread**

Formerly it was thought that extension or progression of the disease in this way was not rare Some recent reports however suggest that longitudinal spread of the disease is really not so common In the report of Sloan et al (1953) progression in the extent of longitudinal involvement was recorded in only 9 2 per cent of cases Excluding those patients who already had involvement of the entire colon when first examined by us there were 62 cases in which longitudinal spread was possible during the period of follow up of 3 years or more Thirty of these (47 per cent) showed radiological evidence of longitudinal spread The incidence of longitudinal spread in relation to the various initial anatomical types is given in Table III Longitudinal spread is infrequent in topographical types uch as enterocolitis and regional colitis The less frequent occurrence of longitudinal spread in these so called segmental types of ulcerative colitis closely simulates the behaviour of regional enteritis where longitudinal spread is very unusual

patients in this R RS group were catalogued as instances of the remitting and relapsing clinical variety of ulcerative colitis There were no examples of the acute fulminating variety of ulcerative colitis in this sub group R RS

*Left colon*

All instances of ordinary distal colitis with colonic involvement extending proximal to the diseased rectum and sigmoid but distal to the hepatic flexure are included in the category *left colon* (21 per cent) The clinical type of disease most often seen in patients with involvement of only the left colon is the remitting variety *In our experience there are very few instances of the acute fulminating* or of the chronic continuous types of disease in the topographical type *left colon* We experienced no medical deaths in this sub group

*Entire colon*

*The entire colon may become involved in two ways In the acute fulminating* type of ulcerative colitis often the entire colon is affected at the time of onset If remission does not take place then the process may continue to smoulder as chronic diffuse inflammation of the entire colon In the non fulminating variety cases are observed in which the primary insult is to the rectum or rectum and sigmoid *With subsequent attacks more and more of the colon becomes affected until* eventually the entire colon is involved This has been referred to as longitudinal spread (*see below*)

In this analysis of hospital material the percentage of cases listed under the category of *entire colon* includes only those in which the entire colon was diseased *at the time of initial study In the group of 182 cases 88 had such involvement* (48 per cent of the entire group) This figure clearly indicates the great number of patients with far advanced disease in our series Ten of the 23 deaths occurring in the 125 cases with long follow up were examples of this topographical sub group (*entire colon*) Surgical treatment was applied eventually in approximately 60 per cent of this group There was a higher incidence of the chronic continuous clinical type of disease in patients with involvement of the entire colon than in any other topographical variety except for type *enterocolitis*

**The regional or segmental type**

The designation regional or segmental type is used for those cases in which some part of the colon but not the rectum is involved (6 1 per cent) The area of involvement may be a long or short continuous segment or it may be two or more separate areas of involvement with a segment of uninvolved bowel intervening Regional or segmental colitis may be quite severe and associated with a relatively high incidence of complications particularly of the systemic variety (Table XI)

**Enterocolitis**

Confusion exists concerning the relative frequency and significance of involvement of the small bowel and particularly the ileum in ulcerative colitis We do not include *instances of characteristic regional enteritis combined with ulcerative* colitis under the heading of ordinary ulcerative colitis Such cases are designated enterocolitis a disease which shows the typical pathological characteristics of

TABLE V

CLASSIFICATION OF CLINICAL TYPES

| | |
|---|---|
| Common type with remissions and exacerbations<br>(*a*) Mild variety | Site of involvement commonly rectum and above<br>Clinical course often mild afebrile<br>Duration of attack after 4-12 weeks (self limited) |
| (*b*) Severe variety (fever toxaemia blood loss) | With complete remission of symptoms and complete resolution of lesion or<br>With complete or almost complete remission of symptoms but continuation of activity by sigmoidoscopy ((*a*) and (*b*) types may merge into chronic continuous type or acute fulminating exacerbation) |
| Chronic continuous type<br>Continuous symptoms without remission for 6 months or longer<br>(Site of involvement commonly rectum and above Entire colon eventually involved) | May be relatively mild without fever<br>All grades of severity (fluctuating often)<br>Usually characterized by progressive deterioration of colon with increasing fibrosis<br>Complications common<br>Irreversible changes eventually occur<br>Surgery usually required |
| Acute fulminating variety | Entire colon usually involved—deep large ulcers<br>Characterized by fever severe toxaemia frequently great blood loss with symptoms and signs often of impending perforation or bowel obstruction |

our entire study group were of the remitting variety *Usually* the reason for recurrence or for the initial attack is not obvious In many instances emotional trauma may have played a role We are confident that because of previous studies in the Graduate Hospital Clinic distorted emotional configurations have importance in the life history and behaviour of this disease (Mahoney et al 1949) Respiratory infection occurred in association with a relapse in a number of patients Other types of stress such as surgical operation and pregnancy seemed to have been provocative in a few others The role of allergy as a significant provocative factor could not be established in our patients with advanced ulcerative colitis

We have been interested in attempting to draw some conclusions concerning the possible effect of the various therapeutic plans that have been used through the years on reducing the duration of attacks or in preventing recurrences in these patients with remissions and relapses It is our impression that the type of therapy employed has not played a dominant role in determining the duration of attacks or in preventing recurrences In many of our patients who were experiencing mild recurrent attacks the episodic attacks seemed to run a self limited course in spite of the type of therapy the same could be said of recurrences

During any given relapse of the disease in the remitting type a remission may fail to occur as it had with all previous attacks that is the remitting type has now changed into the chronic continuous variety This phenomenon occurred in 11 of 84 patients in which the observation was possible an incidence of 13 per cent We have always been concerned for the patient who in previous episodes had experienced a remission within 2–4 months but with a given subsequent attack the *symptoms continue well* beyond the 6 month period The importance of this

TABLE III
TOPOGRAPHICAL DISTRIBUTION AND LONGITUDINAL SPREAD*

| | No of cases | Percentage | Longitudinal spread | |
|---|---|---|---|---|
| | | | No of cases | Percentage |
| Rectum or R S | 10 | 8 | 7 | 70 |
| Left colon | 30 | 25 | 18 | 60 |
| Regional or segmental | 9 | 7 | 2 | 22 |
| Enterocolitis | 13 | 11 | 2 | 16 |
| Total cases | 62 | — | 29 | 47 |

6 c se without compl te n ol m t followed f r 3 ye s o m e w lysed fo l g t d l p d

*In the group of 125 patients with long follow up 61 had involvement of the* entire colon initially and 30 of the remainder showed evidence of extension of the disease while under observation These figures suggest that longitudinal spread does occur in a large percentage of patients who have not already had the entire colon involved during the initial attack

**Clinical varieties in relation to topographical types**

The clinical varieties mentioned are classified below Sixty nine per cent of patients with a long follow up belonged to the remitting variety at the time of onset This clinical variety of ulcerative colitis occurred with about equal frequency among all anatomical types Topographically *enterocolitis* and *entire colon* were the types most often found in patients with the chronic continuous variety of the disease There were 10 instances of acute fulminating disease The latter variety was not seen in enterocolitis and in the distal type of ulcerative colitis involving only the rectum or rectum and sigmoid The entire colon or almost the entire colon was most commonly involved in the acute fulminating variety

## CLASSIFICATION OF CLINICAL TYPES OF ULCERATIVE COLITIS—RELATION TO BEHAVIOUR PATTERNS

*For many years we have utilized a classification of clinical types* as outlined in Table IV Obviously there is considerable overlapping but difficulty is rarely encountered in fitting a given case into this pattern Such a classification serves a useful purpose in orientation and has some importance in prognosis

**Common type with remissions and exacerbations**

This remitting variety is the most common type encountered in the ambulatory *patient who frequently shows involvement of the rectum and sigmoid only* We have mentioned previously that the latter type of out patient often exhibits only mild bleeding and perhaps only slight diarrhoea with mild cramping The attacks are often afebrile and may be entirely unassociated with nutritional deficiency or anaemia Unfortunately in the Graduate Hospital series the milder variety was not often encountered Most of the remitting cases were of sub type (*b*) that is clinical behaviour of moderate or great severity (Table IV) Sixty eight per cent of

**Acute fulminating type**

This is the most dramatic form of the disease the first attack being characterized by an abrupt onset of severe diarrhoea associated with sepsis and rapid depletion of vital tissue constituents as a result of excessive losses from the rectum and of nausea vomiting hyperpyrexia and toxaemia There were only 10 such cases in our entire group of 125 patients with long range follow up Quite a few additional acute fulminating cases were lost to follow up after they had gone into complete remission Outstanding radiological and pathological features of this type of disease include the frequent occurrence of large confluent ulcers and the characteristic involvement of the entire colon or almost the entire colon The complications of pseudopolyposis and acute toxic dilatation of the colon are noteworthy in this clinical type The mortality is high In our small series 30 per cent of those going to surgery and 20 per cent of those not operated upon succumbed This mortality figure for the medically treated cases is probably too high because of the incomplete follow up on the survivors not going to surgery (not included in the survey)

## AGE AT ONSET IN RELATION TO CLINICAL BEHAVIOUR AND PROGNOSIS

**Age at onset of various topographical and clinical types**

Some effort has been made to analyse the behaviour pattern of ulcerative colitis on a basis of age at time of onset This breakdown is given in Table VI There were 12 patients under the age of 15 years and in many of these involvement was either of the entire colon (58 per cent) or the lesion was enterocolitis (25 per cent) In other words extensive involvement was noted in 83 per cent of the children studied There were 66 patients in the group of 125 cases in which the age of on et was from 15 to 29 years In this age span there was a relatively large number with involvement of the rectum sigmoid and left colon and with the regional type Approximately 60 per cent of patients in this age group had rather extensive involvement Between the ages of 30 and 59 years only 47 5 per cent had extensive involvement Perhaps one might conclude that longitudinal involvement of the colon may be less extensive as the age of onset increases

Mention has been made of the relationship between age at onset and type of topographical involvement The remitting type was encountered with about equal frequency at all ages There is a tendency for the continuous type to show a higher incidence with increased age

**Characteristics of the disease occurring in those under the age of 15 years**

In patients with regional enteritis we have been impressed with the high incidence of delayed maturity in those who have contracted the disease before reaching the age of 15 years It is of interest that in ulcerative colitis only 1 of 12 patients in the series exhibited retardation in growth this patient had enterocolitis Defective small intestinal absorption probably plays an important role in this respect in regional enteritis in ulcerative colitis this factor is uncommon and rather unimportant The severity and extent of the disease were greater when it occurred before the age of puberty (5 of the 12 children needed surgical treatment and 3

observation may be noted by consulting Table V Only 11 per cent of 84 patients in the remitting category had attacks extending beyond 6 months yet still experienced a remission therefore it is likely that if a complete remission does not occur within 6 months it may never occur that is the disease has changed to the chronic continuous variety A recognition of this behaviour pattern has considerable clinical importance in the decision concerned with selection of future therapy The majority of patients who experience a recurrence of the disease and whose symptoms continue unabated for longer than 6 months will eventually require surgery

In some instances in the remitting type of disease an attack will apparently terminate that is the patient becomes symptom free and yet the inflammatory process continues to be active as determined by sigmoidoscopy We suspect that many of the so called remissions which occur as a result of steroid therapy belong in this category

An acute fulminating exacerbation of the most severe nature may occur with any given relapse in this remitting type of disease There were 18 instances of severe fulminating attacks among 84 patients belonging to the remitting type of *disease in this series an incidence of 21 per cent*

One of the most curious and serious accompaniments of the fulminant relapse in some patients is that of extreme toxic dilatation of the colon (usually segmental)

TABLE V
DURATION OF ATTACKS IN REMITTING AND ACUTE FULMINATING VARIETIES

| *Duration of attack* | *Acute fulminating* | | *Remitting type* | | *Total cases* |
|---|---|---|---|---|---|
| | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *Number* |
| Under 3 months | 7 | 70 | 34 | 41 | 41 |
| 3–6 months | 2 | 20 | 37 | 45 | 39 |
| 6–12 months | 1 | 10 | 7 | 8 | 8 |
| Over 1 year | 0 | 0 | 3 | 3 | 3 |
| Variable | 0 | 0 | 3 | 3 | 3 |
| Total | 10 | 100 | 84 | 100 | 94 |

**Chronic continuous variety**

This term is applied to those cases in which the inflammatory process remains active well over 6 months Objective evidences of disease continue in spite of treatment Remissions do not occur In the series of 182 cases 47 or approximately 26 per cent were listed as chronic continuous at the time of our first contact with the patient The significant clinical features of this group are summarized in Table IV In the breakdown of clinical types it is noted that approximately 80 per cent of this group had involvement of the entire colon or had enterocolitis Once again it is noted that involvement of the rectum and sigmoid only or the left colon only is not likely to give rise to the chronic continuous type of disease until late in its course The chronic continuous variety shows a high percentage of complications (Table VIII) and a high incidence of necessity for operation Ninety three per cent of this group with a long follow up went to surgery (Tables X and XI)

TABLE VI

AGE OF ONSET OF VARIOUS TOPOGRAPHICAL TYPES—125 CASES

| *Age (years)* | *Rectum and rectum and sigmoid* | | *Left colon* | | *Entire colon* | | *Regional or segmental* | | *Enterocolitis* | | *Total Cases* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *Number* |
| Under 15 | 1 | 8.3 | 1 | 8.3 | 7 | 58.4 | 0 | 0 | 3 | 25 | 12 |
| 15–29 | 5 | 7.6 | 17 | 25.8 | 34 | 51.5 | 3 | 4.5 | 7 | 10.6 | 66 |
| 30–59 | 5 | 11.9 | 12 | 28.6 | 17 | 40.5 | 5 | 11.9 | 3 | 7.1 | 42 |
| 60 and over | 0 | 0 | 1 | 20 | 3 | 60 | 1 | 0 | 0 | 0 | 5 |
| All ages | 11 | — | 31 | — | 61 | — | 9 | — | 13 | — | 125 |

TABLE VII

COLONIC COMPLICATIONS IN RELATION TO TOPOGRAPHICAL INVOLVEMENT—125 CASES

| | *Ordinary distal* | | | | | | *Regional segmental* | | *Enterocolitis* | | *Total group* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *R and R S* | | *Left colon* | | *Entire colon* | | | | | | | |
| | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* |
| Cases followed | 11 | 8.8 | 31 | 24.8 | 61 | 48.5 | 9 | 7.3 | 13 | 10.6 | 125 | 100 |
| Pseudopolyps | 5 | 45.5 | 23 | 74.5 | 43 | 70.5 | 4 | 44.5 | 5 | 38.5 | 80 | 64 |
| Adenomas | 3 | 27.3 | 1 | 3.2 | 6 | 9.8 | 0 | 0 | 2 | 15.4 | 12 | 9.6 |
| Carcinoma | 1 | 9.1 | 1 | 3.2 | 3 | 4.9 | 0 | 0 | 1 | 7.7 | 6 | 4.8 |
| Free perforation | 0 | 0 | 1 | 3.2 | 2 | 3.3 | 0 | 0 | 0 | 0 | 3 | 2.4 |
| Peri rectal disease (abscess and fistula) | 0 | 0 | 5 | 16.2 | 13 | 21.4 | 2 | 22.2 | 3 | 23 | 23 | 18.4 |
| Massive haemorrhage | 1 | 9.1 | 6 | 19.4 | 7 | 11.5 | 1 | 11.1 | 1 | 7.7 | 16 | 12.8 |
| Stricture granuloma obstruction | 2 | 18.2 | 5 | 16.2 | 12 | 20 | 3 | 33.3 | 8 | 46.1 | 30 | 24 |

died) Jackman et al (1940) reviewed the cases of ulcerative colitis occurring in children under the age of 16 years at the Mayo Clinic Their experience was some what similar to ours More children had fulminating symptoms at onset than adults and the incidence of complications including carcinoma was greater in children

**Features of the disease occurring after the age of 60 years**

Only 5 patients in this age group fulfilled our criteria for review (Table VI) The disease at onset was classified as mild in 2 moderately severe in 2 and severe in 1 However 3 of the 5 eventually went to surgery without mishap and 1 of the remainder died without operation Three were of the remitting clinical type and 2 were of the continuous variety The entire colon was involved in 3 cases Only 1 9 per cent of 1 291 cases reviewed by Brust and Bargen (1935) were over the age of 60 years In many of these patients the disease was rather mild Banks et al (1953) reviewed 20 cases of ulcerative colitis beginning after the age of 50 years They concluded that the disease in late life is just as serious and the prognosis just as bad as in younger patients Our experience tends to support that conclusion

## OTHER REMARKS ON CLINICAL BEHAVIOUR

Severe clinical configurations may be anticipated in hospital patients One of these is extreme toxaemia with hyperpyrexia which occurred in 16 per cent of our patients and was confined to the primary acute fulminating type or the acute fulminating relapse Extreme nutritional deficits (haemoglobin albumin calcium potassium sodium prothrombin and so on) were recorded in 14 per cent of patients and were associated most often with excessive faecal losses of mucus and pus and of blood

*Plasma protein deficits may be severe in patients whose faecal discharges contain* excessive amounts of mucus and pus even when loss of blood is minimal Massive bleeding associated either with shock or requiring numerous transfusions was present in 16 instances or 12 8 per cent of patients All of these phenomena were noted most often in the acute fulminating type of the disease or in the fulminant relapse of the chronic varieties

## COMPLICATIONS

Tables VII and VIII list the incidence of colonic complications in the Graduate Hospital series It is noted that they are representative of the type and percentage of complications to be anticipated in the more severely ill patients who may be admitted to a special service of a general metropolitan teaching hospital The incidence of some of these complications is much higher than that encountered in other reports of material derived from some private clinics or from mixed *hospital cases and out patients*

**Pseudopolyposis**

Pseudopolyposis heads the list of local complications and was noted in 80 out of 125 patients or 64 per cent of the entire group In the topographical grouping of cases (Table VII) this complication is seen least often in enterocolitis (38 5 per

**Granuloma stricture or partial obstruction**

There were 30 instances of granuloma stricture or partial obstruction of the colon (24 per cent) Usually these lesions have in common chronic perforation often into the mesocolon Pericolitis with adhesion to other structures is not rare These complications were noted most often in topographical types designated as enterocolitis and regional colitis Operative treatment is required eventually in most instances

**Peri rectal or peri anal disease**

Peri rectal or peri anal disease (abscess and fistula) was encountered in 18 per cent of patients All topographical types showed about the same percentage incidence of peri rectal disease except for the type with involvement only of the rectum or rectum and sigmoid The chronic continuous clinical variety of disease showed the highest incidence of this complication (28 per cent) The remitting type yielded an occurrence rate of peri anal disease of 17 per cent This complication was not seen in the acute fulminating cases Peri rectal infection in some instances fails to respond to local measures either medical or surgical and radical treatment for the colitis must be carried out on this account earlier than it would have been in the absence of this complication

**Dilatation of the diseased colon**

The term toxic aganglionic megacolon is employed here to describe that dread complication of extreme dilatation of a segment or of the entire diseased colon suggesting almost complete colonic obstruction with impending perforation Actually this complication is associated with an absence of effective colonic motility *The tremendous distension of the colon with gas is not the result of* obstruction The colonic dilatation may last for several days or weeks Liquid faeculent evacuations usually continue to occur commonly they are involuntary Extreme toxaemia is a constant concomitant In some instances these colons had previously shown a radiological appearance of marked narrowing and fibrosis often for many years yet with the fulminant relapse the colon may dilate to 4 times the size of a normal colon There were 7 instances of this complication in our series of 125 patients with long follow up (Tables VIII and XII) Among 87 cases classified as belonging to the remitting type there were 18 instances of an acute fulminating relapse of the disease Toxic dilatation of the colon occurred in 4 of these an incidence of 22 per cent among fulminating relapses This complication appeared in 3 of 10 patients during a primary acute fulminating attack

Analysing the 7 cases of toxic colonic dilatation (Table XII) it is noted that 2 patients died both post operatively 1 patient went to surgery and was cured 1 has remained well for 10 years (acute fulminating type) the other 2 continue to experience relapses of a less severe nature

Madison and Bargen (1951) reported an isolated instance of this condition as fulminating chronic ulcerative colitis with unusual segmental dilatation of the colon This was a fulminating relapse in the remitting type of ulcerative colitis The only comprehensive paper dealing with toxic dilatation of the colon is that of Lumb et al (1955) whose experience with 7 cases has been identical with ours in practically every respect We have used the designation toxic aganglionic megacolon to describe this clinical configuration perhaps without sufficient

cent) regional colitis (44 5 per cent) and the rectosigmoidal type (45 5 per cent) Several years ago Beaman reviewed our cases of ulcerative colitis segregating the group with pseudopolyposis in order to compare them with the remainder of cases not having this complication In this study it was clearly shown that the occurrence of pseudopolyposis indicates greater severity of the disease and definitely worsens the prognosis A greater number of patients with this complication experienced severe anaemia from blood loss Nutritional deficiency was more striking Opera tion was eventually required in a greater number of persons The over all mortality was higher in the pseudopolyposis group

TABLE VIII

COLONIC COMPLICATIONS IN VARIOUS CLINICAL TYPES—125 CASES

| | *Remission relapse* | | *Chronic continuous* | | *Acute fulminating* | | *All types* | |
|---|---|---|---|---|---|---|---|---|
| | *No of cases* | *Percent age* | *No of cases* | *Percent age* | *No of cases* | *Percent age* | *No of cases* | *Percent age* |
| Total cases | 87 | 69 | 28 | 23 | 10 | 8 | 125 | — |
| Pseudopolyposis | 51 | 58 | 21 | 75 | 8 | 80 | 80 | 64 |
| Adenomas | 9 | 10 | 3 | 11 | 0 | 0 | 12 | 9 6 |
| Carcinoma colon | 3 | 3 | 3 | 10 | 0 | 0 | 6 | 5 |
| Peri anal disease | 15 | 17 | 8 | 29 | 0 | 0 | 23 | 18 |
| Stricture granuloma obstruction | 19 | 22 | 9 | 32 | 2 | 20 | 30 | 24 |
| Toxic aganglionosis | 4 | 5 | 0 | 0 | 3 | 30 | 7 | 6 |
| Free perforation | 2 | 5 | 0 | 0 | 1 | 10 | 3 | 2 |
| Large penetrating ulcer (Radiological evidence) | 8 | 9 | 5 | 18 | 3 | 30 | 16 | 13 |

I I d s nly p t t who d d w ope t d po o wh h d 3 ye foll w p

## Carcinoma

The designation adenomas in Tables VII and VIII applies to a diagnosis made by the sigmoidoscopist or the radiologist or both but not confirmed in most instances by the pathologist We believe there remains some doubt concerning the influence of ulcerative colitis on the incidence of colonic adenomas The question is worthy of careful review by pathologists interested in ulcerative colitis and its relation to carcinoma There were 6 instances of carcinoma 3 in the chronic continuous and 3 in the long standing remitting types of disease This gives an over all figure of 4 8 per cent for the series

The carcinomatous lesions were advanced when discovered so that the initial morphological type of the tumour whether beginning as a simple adenoma or not could not be determined The occurrence of carcinoma in our patients seemed to bear no relationship to pseudopolyposis There is no justification for recommending operation in the presence of pseudopolyposis with the thought that the danger of carcinoma is greater in such cases It is highly likely that the increased incidence of carcinoma in ulcerative colitis is more closely related to duration of disease and to its clinical type We believe the danger is greater in the patient with chronic con tinuous symptoms of many years duration than in the type with remissions and relapses

TABLE X

END RESULTS—BASIS OF CLINICAL TYPES—125 CASES

| | *Remission relapse* | | *Chronic continuous* | | *Acute fulminating* | | *All types* | | *All types*† | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* |
| Total cases | 87 | 69 | 28 | 23 | 10 | 8 | 125 | — | 187 | — |
| Surgically treated | 41 | 47 | 26 | 93 | 6 | 73 | 73 | 58 | 73 | 40 |
| Surgical deaths | 8 | 9 | 5 | 18 | 3 | 30 | 16 | 13 | 16 | 7 |
| Medical deaths | 4 | 5 | 1 | 4 | 2 | 20 | 7 | 6 | 7 | 4 |
| Total mortality | 12 | 14 | 6 | 22 | 5 | 50 | 23 | 18 | 23 | 13 |
| 3 year cure (medical) | 4 | 5 | 0 | 0 | 1 | 10 | 5 | 4 | | |
| Improved | 2 | [illegible] | 0 | 0 | 2 | 20 | 4 | 3 | | |
| Worsened | 14 | 17 | 1 | 4 | 0 | 0 | 15 | 12 | | |
| Condition unchanged | 21 | 24 | 1 | 3 6 | 0 | 0 | 22 | 17 | | |

I l d ly d th p t f ll w p l g th 3 y rs
† Add t 157 p t t dd d l tt f ll p f ll p l th 3 y ( k w pe t d h)
T h d d

TABLE XI

END RESULTS—BASIS OF TOPOGRAPHICAL TYPES—125 CASES

| | *Rectum and sigmoid* | | *Left colon* | | *Entire colon* | | *Regional or segmental* | | *Enterocolitis* | | *Total cases* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* | *No of cases* | *Percentage* |
| Total cases | 11 | 9 | 31 | 25 | 61 | 49 | 9 | 7 | 13 | 11 | 125 | 100 |
| Surgically treated | 3 | 4 | 17 | 23 | 35 | 48 | 6 | 8 | 12 | 16 | 73 | 58 |
| Surgical deaths | 2 | 13 | 7 | 44 | 5 | 32 | 1 | 6 | 1 | 6 | 16 | 13 |
| Medical deaths | 1 | 14 | 0 | 0 | 5 | 72 | 1 | 14 | 0 | 0 | 7 | 6 |
| Total mortality | 3 | 13 | 7 | 30 | 10 | 44 | 2 | 9 | 1 | 4 | 23 | 18 |
| 3 year cure | 1 | 20 | 0 | 0 | 4 | 80 | 0 | 0 | 0 | 0 | 5 | 4 |

justification This was done in order to indicate that its development may depend upon destructive changes in the nerve plexuses of the diseased colon particularly the myenteric plexus In this connexion the statement which appeared in an article by Storsteen et al (1953) is of interest Two cases were rejected because of excessive destruction and distortion of the myenteric plexus by inflammation In nearly all other cases the myenteric plexus was remarkably well preserved in spite of severe inflammation of the intestinal wall elsewhere Perhaps the very infrequent occurrence of the complication under discussion may be explained by the fact that it is due to destruction of the myenteric plexus since such destruction rarely occurs in ulcerative colitis Histological examination of the dilated segment in 1 of our cases showed complete absence of the ganglionic plexuses in the sub mucosa and muscular layer in many sections with striking degenerative changes in the nerve plexuses in other areas

We suspect that one should avoid operation if at all possible during the phase of acute toxic dilatation of the colon Bowel antisepsis and complete rest of the ali mentary tract with parenteral nutrition should offer the greatest chance of riding out the storm Corticotrophine and steroids may likewise prove dangerous be cause of the risk of perforation or active bleeding

## Marginal ulcers

Another finding to be anticipated in the more severe fulminating disease is the occurrence of large marginal ulcers seen radiologically and present in 13 per cent of our patients (Table IX) This radiological configuration is rarely seen except in the acute severe toxic flare up and in the acute fulminating type of the disease The demonstration of such lesions in the acute fulminating type of ulcerative colitis is an indication for the employment of the most rigid colonic rest regimen (Bockus 1952) and a contra indication to the injudicious use of ACTH or adrenal steroids because of the danger of perforation

TABLE IX
RADIOLOGICAL CHANGES IN RELATION TO CLINICAL TYPES—125 CASES

| *Radiological changes in colon* | *Acute fulminating* | | *Remitting* | | *Chronic continuous* | | *All types* | |
|---|---|---|---|---|---|---|---|---|
| | *No of cases* | *Percent age* | *No of cases* | *Percent age* | *No of cases* | *Percent age* | *No of cases* | *Percent age* |
| Total cases | 10 | — | 87 | — | 28 | — | 125 | — |
| Narrowing | 8 | 80 | 58 | 67 | 22 | 78 | 88 | 70 |
| Shortening | 4 | 40 | 40 | 46 | 17 | 61 | 61 | 50 |
| Haustra absent | 2 | 20 | 49 | 57 | 24 | 86 | 75 | 60 |
| Obstruction or granuloma | 2 | 20 | 18 | 20 | 8 | 29 | 28 | 22 |
| Multiple large discrete ulcers | 3 | 30 | 8 | 9 | 5 | 14 | 16 | 13 |

## Free perforation

Free perforation occurred in 3 patients (2 per cent) One of these was under the age of 15 years Topographically the entire colon was involved in 2 of the patients and the left colon in 1 In one instance the perforation occurred in the acute fulminating type of disease and in the others it occurred during a fulminating relapse of the remitting type

matological disorders that is erythema nodosum pyoderma gangrenosum and non specific pustular eruptions The occurrence of severe spreading pyoderma gangrenosum (associated ordinarily with anaerobic streptococcal invasion) has evidently been greatly lessened since the advent of antibiotics

*Other systemic complications*

Eye complications (iritis and so on) were infrequent and not intractable Severe psychotic reactions (not drug induced) occurred in 3 patients An episode of depression is particularly to be feared fortunately such reactions are uncommon Systemic complications seemed to be most common in the regional or segmental types and least frequent in enterocolitis The relationship between the incidence of systemic complications and the clinical type of disease at onset was not significant

**Previous ACTH or cortisone therapy**

The results obtained with corticotrophin and adrenal steroids in the management of the various types of ulcerative colitis in our clinic have not as yet been analysed We doubt if these agents are of much benefit in the over all long range management of most patients It is probable that the 5 year cure rate is not materially affected In some instances temporary benefit is achieved In others the clinical status is worsened and complications are induced More time is needed before a final evaluation can be made In this present study 18 patients were encountered who had been treated with either ACTH or cortisone prior to admission to the Graduate Hospital The most frequent colonic complication in this group was pseudopolyposis (72 per cent) a greater incidence than among our very seriously ill patients who had not received steroids or corticotrophin There were 2 patients with massive haemorrhage an incidence of 11 1 per cent Fourteen patients in this group were eventually operated upon (78 per cent) 3 succumbed a mortality of 21 per cent These figures may be compared with the percentage of the entire series of 182 patients going to operation—that is 40 per cent—with an over all surgical mortality of 7 per cent One of the surgical cases in the steroid group was an example of acute fulminating toxaemia and another had a so called toxic aganglionic megacolon An additional number of these patients experienced a very stormy convalescence following operation There were 2 instances of acute staphylococcal enterocolitis in the post operative period (Frobese and Roth 1957) Evidently patients who have been on steroid therapy without lasting benefit constitute a more seriously ill group than a comparable control group who have not been so treated Hayes and Kushlan (1956) report a similar experience

## SUMMARY

In order better to understand the factors which may affect the clinical behaviour the incidence of complications and the prognosis in ulcerative colitis our group has recently analysed the cases occurring on the Gastroenterologic Service at the Graduate Hospital Particular attention was given to the influence of the different topographical and clinical types of the disease on its clinical course

It should be mentioned that the sample which i quoted may not be representative of case material collected from private practice or private clinics In most

TABLE XII

TOXIC (SEGMENTAL) DILATATION OF THE COLON

| | *Acute fulminating* | *Fulminating relapse* | *Total* |
|---|---|---|---|
| Number of cases | 3 | 4 | 7 |
| Dilated transverse colon | 1 | 2 | 3 |
| Dilated entire colon | | 2 | 2 |
| Dilated ascending and transverse colon | 2 | | 2 |
| Duration of antecedent disease and topographical type | 42 days (entire)<br>1 month (left colon)<br>*1 month (entire)* | 13 months (left colon)<br>4 years (regional)<br>*7 years (R R S)*<br>14 years (entire) | 7 |
| Operation | | | |
| Recovery | 1 | 1 | 2 |
| Died | 1 | 1† | 2 |
| Cure | | | |
| *Medical (10 years)* | *1* | | *1* |
| Recovery acute phase remitting | | 2 | 2 |

Had te o d p u ly † H d t d p ly ‡ A o et o when fi st e m d

## Systemic complications

The incidence of systemic complications in our patients does not differ materially from that of reports from similar institutions elsewhere

### *Arthritis*

Arthritis occurred in 22 per cent of patients being of approximately the same incidence in the various clinical and topographical types

### *Liver disease*

Liver disease as a complication of ulcerative colitis has been noted by many observers (Kleckner et al 1952) Our experience with hepatic cirrhosis as a complication of ulcerative colitis was previously reported (Tumen et al 1947) In this present review the incidence of liver disease was 10 per cent and included only instances of fatty liver and cirrhosis found at autopsy and cases with high grade bromsulphalein retention A demonstration of associated liver disease is a signal for renewed efforts to achieve and maintain a normal nutritional status particularly as this applies to proteins blood and vitamins If concomitant sepsis renders this impossible of attainment then radical colectomy will need to be considered seriously

### *Thrombophlebitis*

Thrombophlebitis not post operative occurred in 10 per cent of patients Anticoagulants if deemed necessary in the treatment of this complication will need to be used very judiciously because of the danger of inducing massive colonic haemorrhage

### *Skin complications*

Samitz and Greenberg (1951) have previously reported the incidence of skin complications in ulcerative colitis occurring on our service at the Graduate Hospital The present percentage (12) comprises instances of the more severe der

in the fulminating relapse of the remitting type that one notes most often large deeply penetrating ulcers and acute toxic dilatation of the colon complications which add greatly to the severity of the attack

The onset of ulcerative colitis before the age of 15 years entails a graver prog nosis than onset later in life Evidences of neuroticism are often more striking extent of involvement is greater acute fulminating symptoms are more frequent and the incidence of complications is increased The occurrence of the disease after the age of 60 years is rather uncommon Our experience and that of Banks et al (1953) suggest that the clinical behaviour and prognosis of the disease in late life does not differ materially from the average behaviour of the disease at all ages

Patients who had been treated previously with ACTH and cortisone without lasting benefit constitute a more seriously ill group The incidence of complica tions of need for operation and of post operative compl cations was greater in those who had previously had such therapy

The important colonic complications in our patients comprise pseudopolyposis 64 per cent carcinoma 4 8 per cent chronic perforation granuloma stricture and so on 24 per cent peri rectal abscess and fistula 18 per cent massive haemor rhage 12 8 per cent and free perforation 2 per cent The relationship between incidence of complications and the various topographical and clinical types of disease has been briefly discussed The high incidence of local complications is noteworthy

The topographical and clinical varieties of the disease seemed not to influence to any great extent the percentage incidence of the various systemic complications These complications include arthritis skin lesions liver disease thrombophlebitis and psychotic reactions

The severity of the disease in our hospital series is further reflected by an analysis of end results (Tables X and XI) Our figures are not dissimilar to those of Kirsner et al (1954) as a result of a study from a similar type of institution in Chicago This present study adds support to the thesis that ulcerative colitis must be considered a grave disease at all times True there are many patients who ex perience only mild episodic attacks who never become seriously ill or debilitated and do not require hospitalization Futhermore medical cures do occur both in the mild remitting and in the acute fulminating varieties of the disease However one should always have in mind that even those patients with slight involvement of a mild degree may at any time either develop an acute fulminating relapse which may terminate fatally or experience a severe complication requiring radical opera tion The physician charged with the responsibility of treating ulcerative colitis should have been thoroughly indoctrinated in its many intricacies A satisfactory liaison with patient and family is essential The decisions concerning selection of therapy including psychotherapy are often critical and may be exceedingly difficult to make In the use of new agents the danger of deleterious side effects must be ever in mind The decision concerning operation often requires the most seasoned judgement

## ACKNOWLEDGEMENT

The author has drawn freely from the paper Ulcerative Colitis which appeared in *Gastroenterologia* by kind permission of the Editor of that journal

instances the disease was far advanced probably comparable to that seen in other metropolitan teaching hospitals in the north eastern and north central part of the United States of America The impressions based upon this recent study are briefly summarized

The ordinary type of ulcerative colitis in which the rectum participates in the disease process accounted for 85 per cent of cases The entire colon was diseased in almost 50 per cent of the cases studied The latter topographical type accounted for about 50 per cent of the fatalities Operation was required in 60 per cent of this group a high incidence of the chronic continuous clinical type of disease was noted

A relatively small number of our hospital cases (14 8 per cent) had only rectal or recto sigmoidal involvement There were no instances of the acute fulminating disease among those with involvement confined to the distal colon (R RS) This topographical type was most often associated with the remitting clinical type of disease

Although the regional or segmental types are not common nevertheless they are associated with a rather high incidence of both colonic and systemic complica tions Because of the absence of rectal involvement and the ability to perform an operation with internal anastomosis and because of a lack of complete permanent resolution of inflammation in most instances operation is usually performed earlier than in patients with ordinary ulcerative colitis The colonic involvement in enterocolitis similarly is segmental usually sparing the rectum so that ordinarily an internal anastomosis is possible when operation is decided upon A recurrence of disease in the ileum within 5 years may be anticipated in at least 50 per cent of patients with enterocolitis However typical non specific regional enteritis is not seen as a recurrence following operations performed for ordinary ulcerative colitis

A high incidence of patients (47 per cent) with incomplete involvement of the colon when first examined may be expected eventually to experience longitudinal spread of disease Our data suggest that the initial extent of disease longitudinally may be less as the age at onset increases The initial extent of disease to be antici pated is probably greater in the age group of less than 15 years

The most common clinical type of disease is that with episodic attacks or with remissions and relapses (68 per cent) Often the milder attacks seem to run a self limited course regardless of ordinary therapy An attack lasting much longer than 6 months may mean that the clinical course has changed to become chronic continuous that is remissions will no longer occur This change was noted in 13 per cent of cases and is a bad prognostic sign An episodic attack in the remitting variety of disease may at any time be of such severity that it must be termed a severe fulminating relapse simulating in severity the dreaded acute fulminating (single attack) type of the disease This occurred in 21 per cent of our remitting cases

The chronic continuous type of disease—fortunately less common (26 per cent) —is usually associated with involvement of the entire colon and shows a high inci dence of complications and a great need for eventual surgical treatment (93 per cent)

The clinical variety termed the acute fulminating type—relatively uncommon (8 per cent)—is the gravest clinical type The mortality is high both with surgical (30 per cent) and medical treatment (20 per cent) It is in this clinical variety and

# II THE PATHOLOGY OF ULCERATIVE COLITIS

GEORGE LUMB

## INTRODUCTION

ULCERATIVE colitis is a disease of unknown aetiology which most frequently affects the sigmoid colon rectum and distal part of the descending colon It may spread to involve the entire large bowel and less commonly the terminal ileum It is characterized by ulceration of the mucosa and submucosa with subsequent repair by fibrosis which leads to shortening and narrowing of the colon Sydenham (1688) who had earlier described in detail the bloody flux stated that some times though very rarely it happens that a dysentery not rightly cured originally shall afflict a particular patient for many years Wilks and Moxon (1875) intro duced the term ulcerative colitis when they made an attempt to isolate it from more specific forms of dysentery With the advance of bacteriology and para sitology the specific identification of bacillary and amoebic dysentery has become possible but although some have felt that ulcerative colitis is nothing more than a chronic form of bacillary dysentery at the present time most authorities feel that it is a condition which merits separation

Some authors (Brooke and Cooke 1951 Brooke 1954) have attempted to separate the small group of cases which originate on the right side of the colon and which have previously been designated right sided colitis by Crohn and Rosenak (1936) and Crohn (1949) They have used the term ileo colitis in order to stress its importance as a separate entity in view of the different treatment required in this condition Brooke (1954) has also suggested the term procto sigmoiditis for those cases where disease remains localized in the distal sigmoid colon and rectum The pathological appearances of these variants however differ in no way from other types of ulcerative colitis

### Distribution

The extent and site of lesions in ulcerative colitis present an interesting problem It is frequently stated that the disease commences in the rectum and distal sigmoid colon where it may remain localized or spread to involve the entire colon and even the terminal ileum It is true however that the distal colon is more readily examined than any other part and by the time an operation or autopsy specimen is examined widespread involvement may make the decision as to the site of origin very difficult It has been suggested that the whole of the large bowel may be affected by the disease simultaneously without subsequent spread (Warren and Sommers 1949)

It is difficult to obtain adequate proof for one or other theory but examination of 130 operation specimens seen in the Gordon Hospital for Diseases of the Rec tum and Colon London suggests that spread can occur In 10 per cent of cases in this series the right side of the colon was involved first but spread occurred to the distal colon later In the majority of cases the most extensive lesions are seen in the sigmoid colon and rectum the lesions gradually diminishing towards the

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## MACROSCOPIC APPEARANCES

Ulcerative colitis is a disease which exhibits periods of activity with ulceration mucosal congestion and pus formation alternating with periods of remission when mucosal healing and fibrosis take place Macroscopic appearances at any particular time therefore show considerable variations which may be listed as follows

**Group 1**

This group comprises acute progressive lesions with widespread ragged superficial ulcers rarely penetrating deeper than the submucosa The intervening mucosa is intensely congested and shows small punctate erosions appearing as small

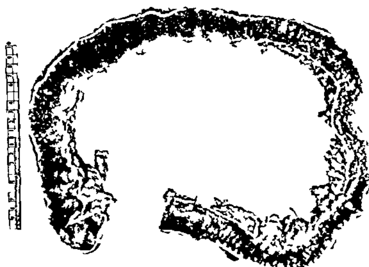


Fig 97—Total colectomy specimen showing diffuse ulcerative colitis with marked pseudo polyp formation

haemorrhagic spots In some cases these areas of mucosa may form projecting tufts known as pseudo polyps (Fig 97) On examination these polyps are found to be of 3 types

(*a*) Ragged mucosal remnants showing oedema and congestion with varying degrees of inflammatory cellular infiltration of the lamina propria These seem to represent nothing more than areas of mucosa remaining after extensive ulceration (Fig 98) They may tend to project into the lumen more markedly as a result of fibrous contraction in the surrounding damaged areas

(*b*) Granulomatous polyps which are heaped up areas of granulation tissue in which may be found occasional fragments of mucosal structure

These 2 types of polyp are very difficult to distinguish on naked eye examination and may be intimately mixed in an area where polyps are found

(*c*) Very occasionally some of the polyps result from active hyperplasia of muco

ileo caecal junction In 89 of the 130 specimens of the Gordon Hospital series the entire colon was involved by the disease In 53 cases the process showed a *sharp* line of demarcation between normal and abnormal mucosa at the ileo caecal valve In 36 cases the distal ileum was affected (Fig 96)

Crohn (1949) and Brooke (1954) have suggested that ileal involvement is due to back wash of infective material from the colon and Brooke has stressed the value of the ileo caecal valve in retarding spread of disease into the ileum He



FIG 96—Incompetent ileo-caecal valve with involvement of the *terminal ileum in ulcer*ative colitis

*pointed out that the valve is non functional in all those* cases where the ileum is affected No example has been seen in this series where spread has taken place without damaging the valve but whether the cause of the mucosal changes in the ileum is in fact the result of back wash of colonic material or whether it represents merely a progression of the inflammatory process with temporary retardation at the ileo caecal valve has yet to be decided

The appendix shows changes similar to those seen in the rest of the colon in approximately 60 per cent of cases

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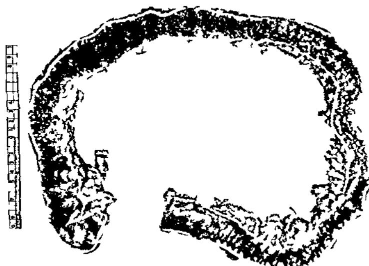


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sal elements This appearance has been noted on only 3 occasions in the series which the author has studied and there seems no evidence that it is the mechanism by which malignant change occurs

The acute inflammatory process may occasionally spread to involve the underlying structure of the bowel wall Destruction of the muscle coats will lead to perforation and sometimes dilatation The peritoneal surface of the colon at this stage in uncomplicated cases shows some thickening and increased vascular markings When perforation occurs there is an ensuing sero fibrinous peritonitis In the series personally studied 10 cases have been seen where colonic dilatation was



FIG 98 —Acute ulceration with remnant of mucosa forming pseudo polyp (haematoxylin and eosin × 145 reduced by one third in reproduction)

a striking feature of the disease (Fig 99) Seven of these cases have been reported previously (Lumb et al 1955) This type of lesion most commonly presents as an acute fulminating process but does not necessarily occur at an early stage in the development of the ulcerative colitis In 4 of the 7 cases described the acute process began less than 1 year after the first symptoms whereas in 3 cases it manifested itself more than 5 years after onset Two cases showed a total colitis whilst 5 had no involvement of the caecum and ascending colon None of the cases had disease in the terminal ileum

The general appearance of the colons in the 5 examples which were removed at operation was of extensive thinning of the bowel in the dilated area with marked vascular congestion producing a weeping haemorrhagic mucosa In the 1 chronic case although the bowel wall was thin the specimen was pale and the mucosa was smooth and glistening All the specimens examined showed evidence of acute perforation at the time of operation or chronic adhesions between the colon and the anterior abdominal wall suggesting that perforation had taken place at some

earlier date Dilatation was maximal in the transverse colon on each occasion In 1 case there was generalized widening of the colon whereas in the other examples the lesion was localized

It seems important to draw attention to this condition as a violent and dangerous complication of ulcerative colitis liable to occur at any stage of the disease In view of the fact that most of these cases showed rapidly advancing ulceration and vascular dilatation a careful search was made for evidence of primary vascular disease

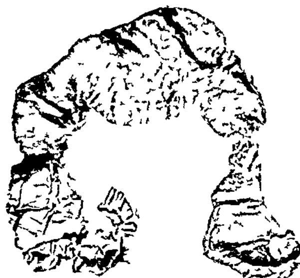


FIG 99 —Total colectomy specimen showing partial involvement of the colon dilatation of the transverse colon and stricture formation in the descending colon in ulcerative colitis

None was found and although occasional examples of thickening of the walls of small vessels in the submucosa could be demonstrated it is felt that these represented a secondary irritative phenomenon

**Group 2**

Areas of ulceration are very frequently found intermingled with zones of healing so that ragged ulcers and pseudo polyps of the types already described are found adjacent to smooth patches of regenerated epithelium A mucosal change frequently seen in association with pseudo polyps is the formation of epithelial bridges where remaining mucosal fragments are seen stretched over denuded areas (Fig 100) The rupture of these strands is probably one of the mechanisms of pseudo polyp formation At this stage of the disease it is common to find commencing thickening of the wall caused partly by oedema and partly by fibrosis The fibrosis is principally submucosal and tends to pull together areas of relatively undamaged mucosa thus minimizing the ulceration and shortening the total length of the colon At the

same time there is a progressive narrowing of the lumen which in areas of maxi mum damage leads to stricture formation (Fig 99) The peritoneal surface shows



FIG 100 — Epithelial bridge over an area of acute ulceration in ulcerative colitis (haematoxylin and eosin × 150 reduced by one quarter in repro duction)

the appearances already described but in addition there is considerable excess fat deposition

**Group 3**

In very chronic cases where damage to the mucosa has been widespread the repair process is inadequate and the colon is lined partly by thin smooth atrophic mucosa and partly by fibrous tissue with underlying fibrous replacement of the muscle wall (Fig 101) Such a colon may be quite thin but when viewed externally may present a relatively normal appearance It should be pointed out that except in cases where there is considerable vascular congestion or where some complica tion such as dilatation or perforation with peritonitis has occurred the external surface of the colon gives very little indication of the degree of mucosal damage This is to be expected as the disease affects principally the superficial mucosal areas but it is important for the surgeon to be aware of this fact when confronted by a relatively normal looking colon at laparotomy in a patient with severe ulcera tive colitis

Group 1 represents the most acute fulminating forms of the disease frequently necessitating surgical treatment The majority of cases of ulcerative colitis show the appearances described in Group 2 Group 3 includes the most long standing forms of this disease which are normally found at autopsy

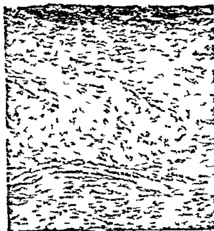


Fig 101 —Total replacement of mucosa by fibrous tissue in chronic stage of ulcerative colitis (haematoxylin and eosin × 200 reduced by one half in reproduction)



Fig 102 —Penetration of the base of a crypt by inflammatory cells to produce an early erosion in ulcerative colitis (haematoxylin eosin × 512 reduced by one half in reproduction)

## HISTOLOGICAL APPEARANCES

### Active disease

The earliest active lesion seems to occur in the bases of the crypts of Lieberkuhn where neutrophils are found passing between the lining cells to accumulate inside the lumen (Fig 102) The basal cells stain poorly their cytoplasm is vacuolated and their nuclei show degenerative changes As necrosis progresses small erosions are produced which establish continuity between the lumen and the submucosa (Fig 102) The accumulation of neutrophils with eosinophils red blood cells serum and mucus in the lumen of the crypts constitutes the so called crypt abscess which is a characteristic feature of the disease (Fig 103) Excessive eosinophil infiltration is an inconstant feature at all stages In the mildest lesions the destructive process may be limited to a portion of the crypt and in such cases it is possible for repair by thin flattened epithelium to occur without loss of normal architecture More commonly however numerous crypts are involved and large areas of their walls break down liberating infective material into the submucosa and producing widespread ulceration These ulcers are very rarely clear cut They usually present an irregular pattern of necrotic debris and inflammatory cells scattered among remaining fragments of viable epithelium (Fig 98)

The inflammatory exudate shows neutrophils only in the most superficial areas In the deeper zones lymphocytes and plasma cells with a smaller number of eosinophils predominate

An additional method of ulcer formation is by the spread of infective material in the submucosa which strips off the overlying relatively normal mucosa producing the so-called lacunal abscess In the majority of cases ulcers are localized in depth at or above the level of the muscularis mucosae

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FIG 104 —Mural vascular dilatation in an area of acute ulceration (haematoxylin and eosin × 115 reduced by one half in reproduction)



FIG 105 —Epithelial regeneration producing flattened cells in ulcerative colitis (haematoxylin and eosin × 135 reduced by one half in reproduction)

## Quiescent disease

The microscopic appearances show an intact mucosa with considerable alteration of its architectural pattern The change is always towards a diminution in the numbers of crypts and generalized thinning following destruction during the ulcerative phase The regular arrangement of crypts which is such a characteristic feature of the normal mucosal pattern is lost when repair occurs Occasional zones of epithelium buried in the underlying submucosa may be found (Fig 106) and even squamous metaplasia may be observed

Goblet cells are seen in larger numbers than normal and mucus secretion is excessive

The cellular infiltration of the lamina propria and submucosa shows the following sequence of appearances

Immediately after an active phase dense accumulations of lymphocytes and plasma cells are found lying below the newly healed epithelium Frequently there is a diffuse infiltration of the muscularis mucosae by lymphocytes and plasma cells which causes fragmentation of the muscle elements Large lymph follicles become apparent as the generalized cellular infiltration diminishes and these are the cause of the granularity of the mucosa as seen through the sigmoidoscope Sheets of eosinophilic mucinous material are seen spread over the irregular mucosal surface If the quiescent phase persists lymphocytes gradually disappear leaving a grossly oedematous lamina propria and submucosa with evidence of dilated lymph channels In cases where the muscularis mucosae has remained relatively intact it may be separated from the mucosa by this wide zone of oedematous connective tissue Considerable numbers of young fibroblasts and capillaries are

The intact cells in the surrounding epithelium differentiate to form increased numbers of goblet cells These cells pour out an excess of mucus which coats the adjacent mucous membrane

The lamina propria is oedematous and the capillaries are dilated and congested This dilatation may be a very striking histological feature and attention has been drawn to it particularly by French authors (Rachet et al 1942 Richir et al 1956) In the most acute fulminating cases dilated vessels may be seen in all coats of the colon but the appearances seem to be nothing more than the vascular response to



FIG 103 —Destruction and dilatation of crypt to produce an isolated crypt abscess in ulcerative colitis (haematoxylin and eosin × 80 reduced by one third in reproduction)

an acute inflammatory process (Fig 104) Bleeding into the ruptured crypts and ulcerated areas is common

The loss of continuity of the surface epithelium gives free access for the normal intestinal flora to enter the submucosa and lamina propria

Damage and repair in the diseased areas tend to go hand in hand so that a single specimen may show all stages from commencing and progressive ulceration in one area to epithelial regeneration and repair in another Vascular granulation tissue infiltrated by lymphocytes plasma cells and eosinophils is formed in the damaged areas Fibrous tissue is laid down which tends to contract and diminish the apparent size of the lesion Epithelial regeneration occurs with the production of flattened cells which grow out from adjacent surviving crypts (Fig 105)

The process of repair may become complete so that the mucosa is reconstituted This state of quiescence may continue for varying periods without further activity During this phase the symptoms may be mild and sigmoidoscopic appearances inconclusive Granularity of mucosa and loss of distensibility are common during this period Less frequently the symptoms may disappear and the sigmoidoscopic appearances may become completely normal

vacuolated cytoplasm breakdown of nuclei and loss of cell outline Numerous neutrophils can be seen passing between these lining cells (Fig 102) The earliest active lesion seems to develop in the bases of the crypts and progresses to produce the characteristic histological changes of the fully developed disease process

The microscopic appearances in the junctional areas between grossly ulcerated and apparently normal mucosa show all the changes already described together with evidence of progression to produce more widespread and more severe inflammatory damage Thus some zones show early cellular degenerative change and small erosions whilst others show frank ulceration with destruction of large numbers of adjacent crypts

In 7 cases islands of typical ulceration were found in areas of mucosa which were otherwise normal These zones consisted of 2 or 3 large ulcers with intervening eroded and injected mucosa sharply demarcated from the surrounding normal colon They show a marked tendency to occur in the lower caecum particularly on the wall directly opposite the ileo-caecal valve (Fig 107) In one case ulceration occurred around the orifice of the appendix and these large foci of disease are designated skip areas The appearances of these lesions both macroscopically and microscopically differ in no way from those typical of ulcerative colitis They are remarkable only for their occurrence at some considerable distance from the main areas affected by disease

Reports in the literature (Levine et al 1951 Jacobson and Kirsner 1956) have suggested that abnormalities in the homogeneous ground substance of the basement membrane of the ep thelial cells might give rise to rupture and abscess formation Sommers et al (1953) when repeating this work felt that any deficiencies in basement membrane which they found were the result of the inflammatory process rather than its cause A personal study has been made of the epithelial basement membrane at the junction between normal and abnormal colon and also in the normal mucosa adjacent to early lesions It is felt that if basement membrane changes are of any significance they should be demonstrable in intact mucosa before erosions or ulcers develop No such changes were found using fresh fixed material from operation specimens stained by the Hotchkiss (1948) P A S method One agrees therefore with Sommers et al (1953) that the deficiencies of basement membrane in the ulcerative phase and the thickening and irregularity which may be seen following repair are post inflammatory changes

Vascular lesions have been suggested by a number of authors as the cause of mucosal damage in ulcerative colitis Gallart Mones (1954 1956) holds the view that the changes are initiated in the submucosa where he states that vascular endothelial desquamation gives rise to submucosal thrombosis with subsequent infarction leading to miliary abscess formation and ulceration Busson and le Quintrec (1954) described "superficial capillary angiectasis" as the earliest change in this disease and without giving any clear-cut reasons stated that "circulatory disturbances play an essential part in the histopathology of the disease" (Busson and Delarue 1956) Warren and Sommers (1949) suggested that a small proportion of cases of ulcerative colitis (19 of their 180 cases) resulted from mucosal degeneration following an inadequate blood supply caused by necrosis and thrombosis of blood vessels in the submucosa and mesentery as in polyarteritis nodosa This condition they called "vasculitis" More recently Ihre (1956) has stated that in about 10 per cent of patients with ulcerative colitis histopathological examination



Fig 106 — Buried epithelium in area of repair in quiescent ulcerative colitis (haematoxylin and eosin × 125 reduced by one half in reproduction)



Fig 107 — Skip area near ileo-caecal valve in ulcerative colitis the main area of disease terminating in the transverse colon in this case

seen in this area and fibrous tissue is gradually laid down A small zone of ulceration may be healed and obliterated completely by fibrous tissue drawing together adjacent areas of mucosa which although abnormal have escaped complete destruction

## THE EARLY LESIONS OF ULCERATIVE COLITIS

When examination is made of those areas of colon where frank ulceration has taken place it is usually impossible to assess the earliest histological changes of the process A recent study has been made of 41 surgical specimens where only part of the colon was involved by disease (Lumb and Protheroe 1956b) When these specimens were studied macroscopically after removal small focal abnormalities could be demonstrated in the areas of colon which at first sight appeared normal in 22 of the 29 cases where total colectomy had been performed (Fig 99) The junction between normal and abnormal mucosa is never abrupt and in all 41 specimens a gradual change could be seen covering an area of several centimetres where diffuse ulceration gave way to more discrete lesions

When the apparently normal mucosa is examined systematically occasional abnormalities are seen There are isolated crypts of Lieberkuhn plugged with polymorphonuclear leucocytes with a surrounding mild degree of capillary dilatation and infiltration of the lamina propria with lymphocytes The smallest lesions visible to the naked eye in these otherwise normal areas of colon are scattered and punctate varying from tiny red spots to larger erosions and small ulcers surrounded by pale normal looking mucosa The microscopic picture shows single or adjacent groups of crypts distended with pus cells lying in their lumina (Fig 103) The cells lining these crypts show degenerative changes with

## CANCER AND ULCERATIVE COLITIS

There is very little to add to what has been written already on this subject Bargen et al (1954) basing their observations on a series of 1 500 cases of ulcerative colitis seen at the Mayo Clinic stated that carcinoma is 20–30 times more common as a cause of death in this disease than in the population as a whole It seems probable that malignant change occurs more frequently in those who have had colitis for many years (Counsell and Dukes 1951–2 MacDougall 1954)

In the series of 346 cases at the Gordon Hospital 7 have developed carcinoma of the colon In 5 cases the disease had been present for more than 10 years in 1 case for 9 years and in 1 case for 2½ years

A recent comparative study of diverticulitis and ulcerative colitis (Lumb and Protheroe 1956a) showed that the essential difference in the mucosal changes in these two diseases is *the tendency for localization to occur in diverticulitis and* where spreading mucosal damage does exist it is usually of a degree mild enough to allow complete regeneration In ulcerative colitis on the other hand spreading mucosal ulceration is the rule and repair when it occurs is inadequate and tends to produce altered and sometimes frankly bizarre cell forms Dukes (1954) stressed the occasional finding of buried epithelium during repair (Fig 106) It seems reasonable to suppose therefore that this inadequate repair mechanism may be one of the factors in malignant change and may be contrasted with the complete regeneration most commonly occurring in diverticulitis where it is usually accepted that there is no evidence of an increased tendency to the development of carcinoma (Stewart 1931)

## CONCLUSION

Breakdown and death of fully differentiated mucosal lining cells with regeneration and repair by cells at the bases of the crypts of Lieberkuhn is a normal phenomenon The balance of this process must be very finely adjusted so as to allow for the minor traumas to the mucous membrane which normally occur

In the specific inflammatory conditions which affect the colon although widespread superficial damage occurs full and adequate regeneration follows It has been suggested (Felsen 1945) that conditions such as bacillary dysentery *may* sometimes lead to a chronic ulcerative colitis but in our experience if this is true *it must be excessively rare*

The study of the earliest morphological changes in ulcerative colitis suggests that it is unlikely that any specific extrinsic cause of the disease exists It seems more probable that a variety of stimuli both intrinsic and *extrinsic may* be sufficient to produce spreading ulceration of the colonic mucosa in an individual where there is some intrinsic failure of normal epithelial regeneration

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revealed changes of the polyarteritis nodosa type These were either localized to the colon only or found in most organs of the body

A careful personal study of 130 operation specimens and 271 rectal biopsy specimens in which particular attention has been paid to the state of the vessels both in the bowel and in the mesentery has not revealed any cases where it was felt that vascular changes played a primary part in the production of the lesions in the colon Occasional thrombosis and evidence of endarteritis have been seen and sometimes—particularly in the older patients—atheroma has been noted On the basis of this work therefore it would seem that the vascular abnormalities are either secondary to the inflammatory process or coincidental degenerative changes It is conceded that cases of polyarteritis nodosa may produce intestinal lesions but so far no example of this phenomenon has been seen which gave rise to confusion of diagnosis with ulcerative colitis

## RECTAL BIOPSIES

It is perhaps surprising that despite the ease of obtaining rectal biopsies and the considerable experience of this technique which exists in the diagnosis of carcinoma of the rectum (Gabriel et al 1951) it is only in recent years that reports have appeared of its uses in ulcerative colitis (Rachet et al *1942* Lumb and Protheroe 1955) Other workers (Truelove and Richards 1956) have used a suction technique for obtaining mucosal material from the sigmoid colon The results obtained by the two methods appear to be similar but it has been the experience at the Gordon



FIG 108 —Typical appearance of rectal biopsy specimen in a relatively quiescent case of ulcerative colitis (haematoxylin and eosin × 30 reduced by one half in reproduction)

Hospital that the interpretation of the larger pieces obtainable by direct vision rectal biopsy is easier From the clinical point of view it is important to mention that in retrospect none of the 238 patients in whom rectal biopsy has been performed has suffered any ill effect There is no suggestion of any exacerbation of the disease process following biopsy Rectal biopsy is of value as an additional method of diagnosis and it is particularly useful in quiescent phases of the disease when *sigmoidoscopic appearances are most difficult to interpret* The frequency of rectal involvement in the disease and also the inadequacy of mucosal repair which occurs can be demonstrated (Fig 108)

## III SURGICAL TREATMENT OF ULCERATIVE COLITIS

BRYAN N BROOKE

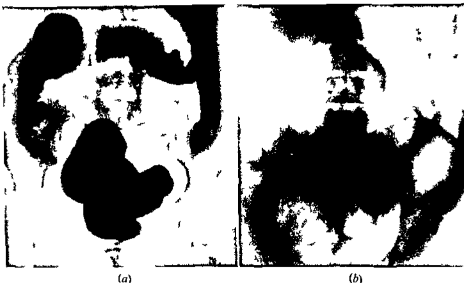
### INTRODUCTION

DURING the last ten years the status of surgery in the treatment of ulcerative colitis has changed Whereas operation was undertaken only as a measure of last resort to avert death it is now recognized as a measure whereby a patient may be restored to full and gainful life As a result the indications for operation have become clarified and widened furthermore with accumulating experience it has proved possible to remove the colon successfully from patients desperately ill from acute complications such as perforation and haemorrhage thus saving further lives hitherto considered irredeemable This change is due to the adherent bag which has enabled ileostomy exudates to be controlled without leakage thus preventing not only incapacity but also the serious discomfort of skin excoriation This improvement has brought with it further problems and a shift in emphasis regarding surgical technique Previously an ileostomy was protected by a box which in no way provided a water tight seal leakage was expected and accepted excision of the colon was at that time the major concern Now with the advent of the adherent bag it is of the first importance that the ileal stoma should be efficient and be capable of proper adaptation to its prosthesis for leakage can no longer be condoned Indeed success or failure of treatment rests almost entirely on the stoma for though the disease is eradicated by ablation of the large bowel the patient will remain incapacitated should the ileostomy fail The technique for fashioning the stoma therefore requires the closest attention and the complications which may render it inefficient must be avoided or be capable of correction It is these matters rather than the manner of removal of the large bowel to which attention must be paid if surgery is to rehabilitate Meanwhile increasing experience has been accompanied by improved judgment as regards the type of cases suitable for operation and the appropriate time for this to be undertaken A better appreciation of pre operative and post operative electrolyte requirements has increased the measure of safety

During the same period controversy has revived regarding the need for a permanent ileostomy resection and anastomosis being favoured by a small group (Aylett 1956) Despite experience both in Great Britain and in America (Gabriel 1953 Cattell 1953) indicating that resection and ileo sigmoid anastomosis is almost invariably followed either by persistence or sooner or later by recurrence of the disease in that part of the large bowel which is retained and by its complications so that further excision and permanent ileostomy become inevitable it is the contention that where ileo sigmoidostomy fails ileo proctostomy succeeds emphasis being laid upon the need to remove the very last inch of colon It is difficult to accept this contention for nomenclature alone differentiates colon from rectum and indeed the upper third of the rectum is misnamed since it develops embryologically as part of the colon Furthermore resection and anastomosis can only be an attractive

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those who are not receiving corticoids but their condition is less likely to deteriorate in this manner and when it does so the circumstances at laparotomy are easier to contend with there being no adhesions unless perforation has occurred and then at one site only no dissolution of the colon wall and less fragility The decision is rendered the more difficult in the light of the fact that remission is initiated or expedited in many patients by corticosteroids (Truelove and Witts 1954 1955) but these drugs should be absolutely contra indicated in patients already distended and are likely to be of little value in the chronic case their administration should cease as soon as it is apparent that no improvement is taking place When surgery is decided upon these drugs should be withdrawn though further administration may become necessary at the time of operation and



(a) (b)

FIG 109 —(a) Barium enema before cortisone treatment (b) straight radiograph of abdomen revealing the degree of colonic dilatation after 6 weeks treatment

immediately afterwards to avoid collapse due to adrenal failure from operative stress supervening in a situation of depletion

Certain acute conditions demand emergency surgery rarely haemorrhage is exsanguinating and calls for immediate colectomy and profuse bleeding may then persist from the rectum alone necessitating its excision also Perforation is best anticipated by colectomy in the stage of impending perforation when the colon in part or whole distends as a result of the weakening of its walls by the combination of infection ulceration and sometimes corticosteroids Very rarely an area of perforation becomes sealed off and the patient survives if such a case is seen in 2 or 3 days after the event it is wise to defer surgery provided it is obvious that deterioration is not occurring Colectomy is required for free perforation since ileostomy alone with attempted suture and drainage seldom averts death Indeed if the colon remains it is likely to perforate again another day sometimes within a week even though the faecal stream has been diverted via an ileostomy

alternative to excision of the whole large bowel so long as ileostomy is incapable of proper management and it is in part due to a failure to appreciate the improvement wrought in this respect that resection continues to be advocated by some

Perforation and exsanguinating haemorrhage *can occur from the rectum* necessitating its excision *ab initio* also remote complications such as arthritis may start due to retention of the rectum following resection and anastomosis and so may carcinoma Uncertainty regarding health must inevitably persist so long as any part of the large bowel remains Resection cannot therefore be regarded as a routine procedure it should be reserved for the rare case in which the rectum is not involved for children until of an age when an ileostomy can be managed and for those with mental deterioration

## INDICATIONS FOR SURGERY

When a patient s condition continues to deteriorate despite all other forms of therapy the time has come for operation this might even be extended to include those patients whose condition remains stationary It is under these circumstances that the decision for surgery is most difficult to make a patient who has been ill for only a few weeks may require operation yet there is a natural inclination for those attending him to hope that improvement may yet occur This Micawber like *attitude is still responsible for a number of otherwise avoidable deaths more* particularly so since the introduction of corticosteroid therapy

A point is reached when continued and severe diarrhoea produces a metabolic disturbance which is irreversible in particular total serum proteins fall with a reversal of the albumin globulin ratio and serum potassium may fall to levels below 3 milli equivalents per litre when such changes can no longer be corrected operation is likely to prove fatal

Cortisone and ACTH now complicate the picture and indeed make the surgical task more difficult and more hazardous These drugs are frequently administered *for too long in patients who show no beneficial response* the intention being to give them a full trial the electrolyte disturbance is increased thereby and at the same time the integrity of the bowel wall is seriously prejudiced with the result that in those patients who do not respond to these drugs atonic dilatation occurs the wall becomes paper thin and prone to perforate and becomes adherent to surrounding structures In some cases the bowel wall is entirely destroyed leaving the abdominal parietes as substitute This condition is accompanied by marked deterioration in the general condition of the patient with rise in pulse rate and temperature by acute abdominal distension due to colonic dilatation (Fig 109) and by pain

The adherence of the bowel—remarkable by its absence in ulcerative colitis untreated by corticosteroids—together with the marked friability of its wall present to the surgeon technical difficulties which on occasion prove impossible to overcome In those cases receiving corticosteroids it is important therefore that the decision *to operate should be made before distension occurs and before temperature* and pulse rate start to rise above their already abnormal levels for to delay is to deny both the patient and the surgeon the proper conditions for success It is wise but less imperative that the decision should also be made at this stage in

## PRE OPERATIVE AND POST OPERATIVE CARE

The most important feature in pre operative care is to bring the patient to ileostomy rather than ileostomy to the patient This is best achieved by explaining that the purpose of operation is to enable the patient to return to full activity and normal life and then indicating the implications of a permanent ileostomy The rest may be left to a former patient it is now possible to use the visiting service arranged by Q T Britain the national ileostomy association for this purpose A visit from

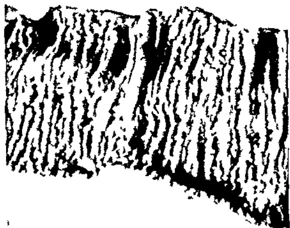


FIG 110 —The small bowel in entero colitis

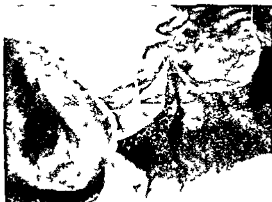


FIG 111 —Ileocaecal valve and terminal ileum in colo ileitis

one who already has an ileostomy provides the most convincing argument in favour of the operation to be undertaken and at the same time ensures an accurate account of ileostomy management

Protein replacement is important before operation since up to 15 grammes of nitrogen may be lost in the stools daily (Posey and Bargen 1950) the plasma proteins are often low with a reversal of the albumin globulin ratio changes which are difficult and sometimes impossible to correct Following ileostomy an average of 2–3 grammes is lost from the stoma in the immediate post operative period

The fulminating disease can be checked by urgent surgery though many advocate colectomy on the logical grounds that toxicity will not be overcome while the colon is retained Ileostomy as the initial step in these cases has proved to have no higher mortality rate (Brooke 1956) than primary colectomy though con valescence is then more protracted

In many chronic cases it eventually becomes obvious that the patient will con tinue to lead a useless existence only until the large bowel has been removed operation is therefore required for anyone unlikely to return to normal life after any other means of treatment That normal life can be attained thereby is proved by results revealed after follow up of patients who have had an ileostomy for a considerable time (*see below*) but in most chronic cases the scales are tipped in favour of surgery by the onset of complications both ano rectal and remote Of the remote complications arthritis affecting mainly the large joints is the common est the condition subsides if the large bowel is removed before delay has caused permanent changes within the joints Erythema nodosum stomatitis and pyoderma gangrenosum a rare complication also respond to excision while iritis also rare will cease but usually not before permanent changes have occurred

In the anal region ulceration is often gross and associated with fistula in women rectovaginal fistula is not uncommon Excision of these local lesions in the usual manner leaves areas which will not heal removal of the large intestine is therefore necessary Stenosis throughout the rectum is sometimes seen frank strictures whether in the rectum or colon make procto colectomy imperative for another reason since carcinomatous change lurks at these sites The possibility of malig nancy is greatly increased in the long standing case so that for any patient who has had ulcerative colitis for 10 years or more removal of the bowel is indicated on this ground alone particularly as no alteration or development of new symp toms other than perhaps pain occurs to reveal that malignant change is taking place Late recognition doubtless accounts for the poor results which have followed excision when carcinoma is present though the prognosis when the condition is revealed radiologically rather than by a clinical change is not entirely hopeless (Brooke 1956) It is also worth noting in this respect that pseudopolyposis cannot be regarded as implying a pre malignant state as some reports have suggested Confusion has arisen with adenomatous polyps in ulcerative colitis the polyps are commonly mucosal tags sometimes granulomas and rarely adenomas The presence of pseudopolyps as revealed by sigmoidoscopy and barium enema should not therefore be taken as an indication in itself for excision of the bowel

## CONTRA INDICATIONS TO SURGERY

Contra indications to surgery are few As already mentioned an ileostomy is to be avoided in children and patients with mental deterioration Enterocolitis (right sided colitis) is a further instance since in this condition the small bowel is involved (Fig 110) making ileostomy inappropriate (Cooke and Brooke 1955) When however the ileum is involved secondarily to true ulcerative colitis (colo ileitis) through breakdown of the ileocaecal valve (Fig 111) ileostomy is successful even when the stoma has been fashioned from a segment which was inflamed (Brooke 1956)

enable the proper use of the adherent bag an instructional film is helpful in this respect Most patients choose to change the bag for the purpose of cleaning once each day sometimes twice but it can be left on for as long as 3 or more days the less frequently the bag is detached the better is the condition of the skin

## SODIUM

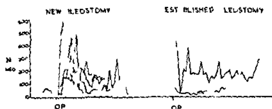



Fig 113 —Sodium excretion from an ileostomy (estimations from 7 cases) Estimations prior to ileostomy are from the diarrhoeic stools

## TECHNIQUE

A recent trend has been towards removing the large bowel *in toto* at one operation whenever possible thus eliminating the rep ated risk of post-operative complications Should the patient s condition be such that a dissection within the pelvis *cannot be undertaken initially* then the choice lies between primary colectomy

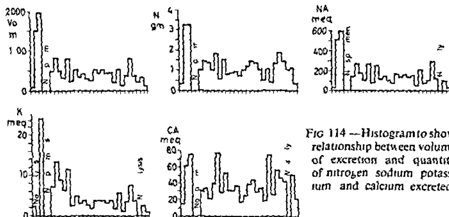



Fig 114 —Histogram to show relationship between volume of excretion and quantity of nitrogen sodium potassium and calcium excreted

followed by excision of the rectum and ileostomy with subsequent panproctocolectomy primary colectomy is preferable as the first stage since this removes at the outset a major part of the source of illness and at the same time makes possible a terminal ileostomy which is technically easier to construct and more satisfactory in outcome At primary colectomy the bowel is divided caudally through the sigmoid and the distal end brought out through the abdominal wound as a non functioning colostomy to be removed later at a synchronous combined excision of the rectum The caudal section may be made at the pelvic floor and the distal

falling to 1 gramme when the stoma is fully established (Fig 112*a*) As regards electrolytes potassium loss is the main pre operative concern the serum potassium falling to figures as low as 2 9 milli equivalents per litre potassium loss is reduced by ileostomy (Fig 112*b*) and the electrolyte problem is then switched to sodium which may be excreted from the stoma at a rate of 200–400 milli equivalents per litre (Fig 113) Potassium replacement is needed pre operatively but post operatively only when *ileostomy disturbance occurs whereas attention must be directed* towards sodium replacement following ileostomy Since sodium loss and the volume output are closely correlated (Fig 114) 300 milli equivalents of sodium should be administered for every litre of fluid excreted When an ileostomy begins

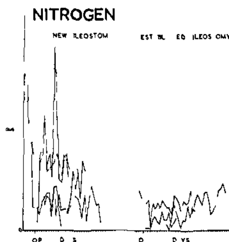



FIG 112*a* —*Nitrogen excretion from an* ileostomy (estimations from 7 cases) The high peak in 1 case occurring 7 days after ileostomy was due to pseudo membranous enteritis *Estimations* prior to ileostomy are from the diarrhoeic stools

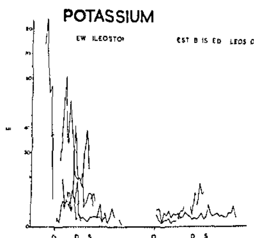



FIG 112*b* —*Potassium excretion* from an ileostomy (estimations from 7 cases) In 1 case the high post operative output at the seventh day was due to pseudo *membranous enteritis in another the* immediate post operative output was high in association with ileitis secondary to the original colitis Estimations prior to ileostomy are from the diarrhoeic stools

to act the volume output is high—from 2 to 3 litres or more daily This falls to 250–500 millilitres daily from the established ileostomy In the post operative period therefore intravenous administration is usually required to restore both salt and fluid in adequate quantity

The skin surrounding an ileostomy becomes *excoriated* very *commonly soon* after its establishment This may be prevented to some extent by covering the surrounding skin with a plastic film (Nobecutane) at the time of operation Alleviation can be obtained with one of the following Baltimore paste zinc cream barrier creams hydrocortisone ointment and silicone cream It invariably heals but will recur with the development of rubber sensitivity or complications such as fistula or recession Before leaving hospital the patient is instructed in the care and management of the *ileostomy in order to avoid excoriation and to*

enable the proper use of the adherent bag an instructional film is helpful in this respect Most patients choose to change the bag for the purpose of cleaning once each day sometimes twice but it can be left on for as long as 3 or more days the less frequently the bag is detached the better is the condition of the skin

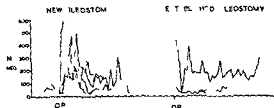



FIG 113 —Sodium excretion from an ileostomy (estimations from 7 cases) Estimations prior to ileostomy are from the diarrhoeic stools

## TECHNIQUE

A recent trend has been towards removing the large bowel *in toto* at one operation whenever possible thus eliminating the repeated risk of post operative complications Should the patient s condition be such that a dissection within the pelvis cannot be undertaken initially then the choice lies between primary colectomy

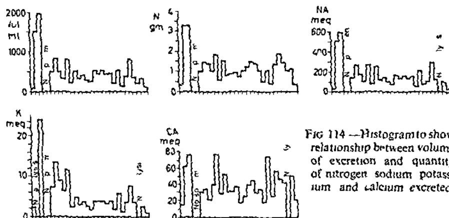


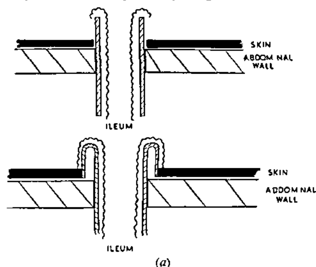

FIG 114 —Histogram to show relationship between volume of excretion and quantity of nitrogen sodium potassium and calcium excreted

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end closed so that the rectal stump can be removed later per perineum this however prolongs the initial operation considerably and leaves within the abdomen a sutured distal end of bowel which may be unsound furthermore perineal excision of the rectum is sometimes rendered difficult by adherence of small bowel to this stump and is usually more disturbing to the patient than a synchronous combined excision

**The ileostomy**

The need to place the ileal stoma at a site appropriate for the accommodation of the bag is now widely appreciated the most common fault in the past having been to place it so low that the flange impinged upon the groin with flexion of the hip causing it to become loosened from the skin Mucosal eversion (Brooke 1952) is now widely practised in both Great Britain and the United States of America (Fig 115) and was primarily designed to avoid stenosis which previously occurred




(*a*)

Fig 115—(*a*) Method of mucosal eversion below as compared with simple exteriorization of ileum (*b*) the stoma resulting from eversion (*By courtesy of the Editor of the Lancet*)





(*b*)

in at least 25 per cent of all cases Since employing this technique stenosis has occurred only once in 76 ileostomies Prolapse with its corollary recession is avoided by proper fixation of the mesentery to the parietes within the abdomen

Of 106 patients with ileostomies performed by the present writer and surviving 3 have suffered prolapse and 6 recession Sometimes the mesentery becomes detached as the patient gains weight

Fistula at skin level is a further complication rendering the stoma inefficient it occurs inferiorly and is due to chafing by the flange of the adherent bag—again when the ileostomy is sited too low All such complications can only be corrected by a proper revision of the ileostomy conducted through a separate laparotomy incision measures confined to the ileostomy itself fail are prone to leave scars causing irregularity of the skin and thus impair adhesion of the bag

Intestinal obstruction is a major complication encountered in all clinics (Swinton 1956) and is due partly to the natural incidence of adhesions following abdominal operations in the presence of infection and inflammation and partly to the un natural stoma During the first 7–10 days approximately 25 per cent of patients suffer partial obstruction at the stoma lasting 24–48 hours this seldom requires laparotomy for its relief After the ileostomy has begun to act the complete failure at any period to pass any wind or fluid through the stoma for more than 24–36 hours associated with colic calls for operative relief

## RESULTS

**Mortality rate**

Of 134 patients submitted to the elective procedure of permanent ileostomy and excision of the bowel 11 have had resection and anastomosis for the reasons already given and 3 of these have already required conversion to a permanent ileostomy Thirteen of the total of 145 have died following operation giving a mortality of 8–9 per cent (247 operations have been performed excluding those required for revision of the stoma giving an operative mortality of 5 per cent) Four late deaths have occurred 1 from lung abscess 2 from obstruction and 1 from carcinoma thus the over all mortality following surgery has been 12 per cent a figure in accord with that from the Lahey Clinic (Swinton 1956)

**Post operative adaptation**

A review was undertaken at December 1955 of all survivors with a view to assessing life with an ileostomy 4 were lost to follow up The following questions were put to 101 patients with whom contact could be made

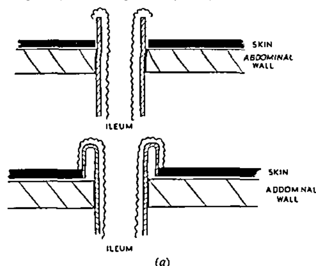
Are you well?
Are you at work at a job or household duties?
How soon after operation did you return to work?
Can you follow your usual pastimes?
Do you find your activities are limited in any way?
Is the ileostomy satisfactory?
What was your weight before operation and what is it now?
Do you limit your diet in any way and if so why?

From the Table it will be seen that of 101 ileostomy patients followed 92 were at full work 7 being convalescent The 2 patients doing no work were nearly blind following iritis 1 having arthritis in addition Five patients did not regard the ileostomy as satisfactory though they did not go so far as to state that it was

end closed so that the rectal stump can be removed later per perineum this however prolongs the initial operation considerably and leaves within the abdomen a sutured distal end of bowel which may be unsound furthermore perineal excision of the rectum is sometimes rendered difficult by adherence of small bowel to this stump and is usually more disturbing to the patient than a synchronous combined excision

**The ileostomy**

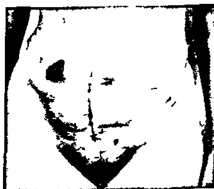
The need to place the ileal stoma at a site appropriate for the accommodation of the bag is now widely appreciated the most common fault in the past having been to place it so low that the flange impinged upon the groin with flexion of the hip causing it to become loosened from the skin Mucosal eversion (Brooke 1952) is now widely practised in both Great Britain and the United States of America (Fig 115) and was primarily designed to avoid stenosis which previously occurred




(*a*)

Fig 115—(*a*) Method of mucosal eversion below as compared with simple exteriorization of ileum (*b*) the stoma resulting from eversion (*By courtesy of the Editor of the* Lancet)





(*b*)

in at least 25 per cent of all cases Since employing this technique stenosis has occurred only once in 76 ileostomies Prolapse with its corollary recession is avoided by proper fixation of the mesentery to the parietes within the abdomen

Of 106 patients with ileostomies performed by the present writer and surviving 3 have suffered prolapse and 6 recession Sometimes the mesentery becomes detached as the patient gains weight

Fistula at skin level is a further complication rendering the stoma inefficient it occurs inferiorly and is due to chafing by the flange of the adherent bag—again when the ileostomy is sited too low All such complications can only be corrected by a proper revision of the ileostomy conducted through a separate laparotomy incision measures confined to the ileostomy itself fail are prone to leave scars causing irregularity of the skin and thus impair adhesion of the bag

Intestinal obstruction is a major complication encountered in all clinics (Swinton 1956) and is due partly to the natural incidence of adhesions following abdominal operations in the presence of infection and inflammation and partly to the unnatural stoma During the first 7–10 days approximately 25 per cent of patients suffer partial obstruction at the stoma lasting 24–48 hours this seldom requires laparotomy for its relief After the ileostomy has begun to act the complete failure at any period to pass any wind or fluid through the stoma for more than 24–36 hours associated with colic calls for operative relief

## RESULTS

### Mortality rate

Of 134 patients submitted to the elective procedure of permanent ileostomy and excision of the bowel 11 have had resection and anastomosis for the reasons already given and 3 of these have already required conversion to a permanent ileostomy Thirteen of the total of 145 have died following operation giving a mortality of 8–9 per cent (247 operations have been performed excluding those required for revision of the stoma giving an operative mortality of 5 per cent) Four late deaths have occurred 1 from lung abscess 2 from obstruction and 1 from carcinoma thus the over all mortality following surgery has been 12 per cent a figure in accord with that from the Lahey Clinic (Swinton 1956)

### Post operative adaptation

A review was undertaken at December 1955 of all survivors with a view to assessing life with an ileostomy 4 were lost to follow up The following questions were put to 101 patients with whom contact could be made

Are you well?
Are you at work at a job or household duties?
How soon after operation did you return to work?
Can you follow your usual pastimes?
Do you find your activities are limited in any way?
Is the ileostomy satisfactory?
What was your weight before operation and what is it now?
Do you limit your diet in any way and, if so why?

From the Table it will be seen that of 101 ileostomy patients followed, [illegible] were at full work 7 being convalescent The 2 patients doing no work [illegible] blind following iritis 1 having arthritis in addition Five patients did not regard the ileostomy as satisfactory though they did not go so far as [illegible]

TABLE

FOLLOW UP FINDINGS

| | *Interval since first operation (years)* | | | *Total* |
|---|---|---|---|---|
| | 5 + | 3–5 | 0–3 | |
| No of patients | 39 | 25 | 37 | 101 |
| Health | | | | |
| Fit | 37 | 23 | 30 | 90 |
| Reasonable | 2 | 1 | 7 conv | 10 (7 conv ) |
| Unfit | — | 1 | — | 1 |
| Work | | | | |
| Full | 38 | 24 | 30 | 30 |
| Limited | — | — | 7 conv | 7 conv |
| None | *1* | *1* | — | *2* |
| Pastimes | | | | |
| Full | 35 | 19 | 25 | 79 |
| *Limited* | *4* | 6 | *12 conv* | *22 (12 conv )* |
| Activities | | | | |
| Full | 25 | 18 | 17 | 60 |
| *Limited* | *14* | 7 | *20 (7 conv )* | *41 (7 conv )* |
| Ileostomy | | | | |
| *Satisfactory* | *38* (4 exc ) | *23* (3 exc ) | *35* (4 exc ) | *96* |
| Unsatisfactory | 1 (leak) | 2 (exc ) | 2 (exc ) | *5* |
| Weight | | | | |
| Gained | 34 | 24 | 32 | 90 |
| Stationary | 2 | — | 3 | 5 |
| *Lost* | *3* | *1* | 2 | *6* |
| Diet | | | | |
| Full | 17 | 11 | 22 | 50 |
| *Restricted* | *19* | *14* | *11* | *44* |
| Unstated | 3 | — | 4 | 7 |

Conv = convalescent exc = excoriation of skin leak = leakage

unsatisfactory nor were they prevented from following full employment 11 *patients who considered the ileostomy to be satisfactory suffer slight or inter* mittent excoriation Most patients were able to follow pastimes of their choice such as swimming dancing tennis The limitation in activity experienced by 34 *patients was due to discomfort on stretching or bending* and sometimes when lifting heavy weights 7 others were still convalescent Approximately 50 per cent of the patients restricted their diet most because fruit skins or pips formed an *indigestible bolus causing colic as it reached the indistensible ileostomy stoma* some found that fruit juices green vegetables or salads caused the motion to become fluid others avoided a large meal in the evening since this might so fill the adherent bag during the night as to require its evacuation 6 patients were

dieting in order to reduce weight which had increased embarrassingly (4 st 7 lb – 12 st 8 lb 8 st – 15 st) It is worth noting that the results remained satisfactory in those treated 5 years or more previously 5 of whom had lived with an ileostomy for 10 years or longer

**Impotence**

The fear has been expressed (Dennis 1945) that removal of the rectum might lead to impotence in the male specific inquiry on this point has shown the fear to be ungrounded though it has not been possible to put the question to every male patient Three women have gone to term and breast fed their babies after normal labour without complications to the ileostomy one of them has had two normal pregnancies

**Future employment of the patient**

One disability has been encountered which arises out of a failure within the medical profession to appreciate the revolution wrought by the adherent ileostomy bag Some patients when applying for jobs have been unsuccessful on medical grounds In contrast to this at least one patient has been accepted as a reasonable risk for life insurance

The results indicate that patients submitted to permanent ileostomy are not incapacitated thereby provided the ileostomy is efficient and designed for the adaptation of the adherent bag In this series only 2 of the 101 survivors are not living a full life and their permanent incapacity arises not from the ileal stoma but from a pre existing complication of the disease If surgery is undertaken soon after the onset of a complication this will be cured and will not recur One indication for surgery has been this that the time has come for operation when a patient appears unlikely to return to *normal* life after any other means of treatment this indication appears to be justified by results

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| Satisfactory | 38 (4 exc) | 23 (3 exc) | 35 (4 exc) | 96 |
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anatomy and it is therefore necessary to define this region Because there is nothing to indicate the position of the rectosigmoid on the large intestine itself it is suggested that the level of the lower border of the sacral promontory be employed to mark this site

After division of any pathological adhesions the large intestine as it passes into the pelvis is gently straightened and the position of the lesion is assessed in relation to the lower border of the sacral promontory A lesion placed entirely above the lower margin of the sacral promontory should be regarded as being in the lower sigmoid colon whereas if it is situated entirely below the level it is considered to be in the intraperitoneal portion of the rectum When situated partly above and partly below the lower border of the sacral promontory or impinging upon it the lesion is classified as rectosigmoid This landmark has been used in the cases recorded

The distance of the sacral promontory from the anus on sigmoidoscopy will of course vary but it is about 17 centimetres in a man of an average height of 5 feet 10 inches

*Choice of operation*

*Combined excision* —In a majority of cases—three quarters—combined excision is the most radical and suitable operation for cancer in this region owing to the situation of the growth and its extent when the patient seeks treatment

The sub-peritoneal portion of the rectum is intimately enveloped by the pelvic fascia and the pubo coccygeus portion of the levator ani muscles For this reason radical removal of a growth at this level can be obtained only by sacrifice not merely of the pelvic fascia but also the musculature of the pelvic floor

The mode of lymphatic spread demands that this operation be employed for *growths situated less than 10 centimetres from the anal orifice and for those placed* below the peritoneal pouch in fact for growths readily palpable on digital rectal examination

Combined excision of the rectum may be performed by the abdomino-perineal method of Miles or the perineo abdominal method of Grey Turner and Gabriel Both these operations require the turning of the patient between the two phases of the operation The perineo abdominal operation however permits the pelvic peritoneum to be more easily closed over an empty pelvis

The use of the Trendelenburg lithotomy position (Bloodgood 1906 Clogg 1923 Devine 1937 and Lloyd Davies 1939) for the performance of combined excision has several definite advantages and has been adopted in all operations for cancer of the rectum rectosigmoid and left colon The position obviates moving the patient during operation and allows a simultaneous and easy access to both the abdominal and the perineal fields Either a two team (synchronous) or a single handed combined excision may be performed or the plan and type of operation altered Precise anatomical dissection of the perineum is possible the levator ani muscles and fascial planes are readily displayed and widely excised and the pelvic peritoneum closed over an empty pelvis

The excision of large advanced growths which often fill the pelvis is easier to accomplish by a dual approach by two surgeons High ligation of the inferior mesenteric artery at its origin from the aorta dissection of ureters and removal of other organs may be carried out whilst the perineal dissection is proceeding

## CHAPTER 20

# THE TREATMENT OF CARCINOMA OF THE RECTUM, RECTOSIGMOID, AND LEFT COLON

C Naunton Morgan

## CARCINOMA OF THE RECTUM AND RECTOSIGMOID

### Spread of carcinoma of the rectum

The work of Cuthbert Dukes and his associates at St Mark s Hospital London and many others has demonstrated that extension of growth in the submucosa of the rectum is very slight and further that retrograde lymphatic spread is uncommon From an investigation of 1 500 consecutive operation specimens Dukes has shown that downward or retrograde lymphatic spread was present in 6 5 per cent but only in 2 per cent for a distance of more than 2 centimetres The primary growth was found to be of a high grade of malignancy in about 75 per cent of the specimens exhibiting downward spread

Upward lymphatic spread along the inferior mesenteric vessels is by far the most constant and frequent pathway

Lateral spread in the pelvic musculature and pelvic fascia is unusual when the neoplasm is situated above the level of the peritoneal pouch (Wood and Wilkie 1933 Sauer and Bacon 1951) In fact the prognosis for a rectal carcinoma with lymphatic metastasis situated above the peritoneal sac is about twice as good as for similar lesions placed below this level Even in the absence of lymphatic spread sub peritoneal rectal carcinomas have a slightly poorer survival rate

Gilchrist and David (1948) found that the incidence of local recurrence was 23 per cent when carcinomas with lymphatic metastasis were situated below the peritoneal reflection whereas with similar growths placed above this level the incidence was 3 6 per cent These facts indicate that lateral spread is more common when the growth is situated in a sub peritoneal portion of the rectum

Venous spread has been found in about 10 per cent of specimens examined at St Mark s Hospital and though venous invasion is unpredictable in over 50 per cent of such specimens the primary growth was of high grade malignancy

From the foregoing observations it is plain that any operation for the cure of cancer of the rectum must allow a wide removal of the upward lymphatic field and in addition the inferior mesenteric vascular pedicle should be ligated early in the operation before the primary tumour is manipulated in order to diminish the chance of embolic spread Furthermore the infrequency of downward and lateral spread in growths situated above the level of the peritoneal reflection supports the view that in suitable cases restorative anterior resection for carcinoma of the intraperitoneal rectum and rectosigmoid is a radical procedure

### Treatment

Anatomically the rectum commences opposite the third piece of the sacrum but identification of this level at operation is difficult and may be impossible The site of the rectosigmoid junction varies according to a surgeon s concept of surgical

(2) The growth should be situated not less than 10 centimetres—by sigmoidoscopic measurement—from the anus and in addition be placed above the level of the peritoneal reflection Though the level of the peritoneum is variable both the sigmoidoscopic measurement and the relation of the neoplasm to the peritoneal reflection *together* afford a useful yard stick for assessment of the site of a neoplasm

(3) When an intraperitoneal rectal growth is advanced with evidence of extra rectal spread or lymphatic metastasis owing to the risk of local recurrence restorative resection should not be performed except occasionally as a palliative measure Restoration of continuity should not be attempted in the presence of a growth of high grade malignancy since both widespread lymphatic and venous

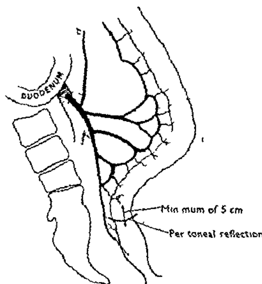



FIG 116—Removal of the upward lymphatic field for carcinoma of the rectum and rectosigmoid

involvement are much more common especially in a retrograde direction An anaplastic neoplasm is to be suspected when there is a submucous tumour with little or no ulceration In such cases a linear infiltration extending from the growth due to involvement of the lymphatics may be palpated in the rectal wall

Pre operative sigmoidoscopic biopsy which is carried out in all cases of carcinoma of the rectum rectosigmoid and distal sigmoid colon may confirm the presence of an anaplastic carcinoma

(4) Resection and anastomosis are unsuitable as a rule in an obese subject with a small pelvis and a fat laden mesentery owing to the operative difficulties and the inability to identify the mesenteric vascular pattern It is unwise to perform a restorative resection if this procedure is going to be a difficult technical feat A short fatty sigmoid mesentery may prevent restoration of continuity except when it is possible to mobilize the transverse colon Anastomosis must be performed without tension and with certainty of blood supply to both bowel ends

Anterior resection is an ideal palliative operation in the presence of hepatic secondaries when the rectal lesion is suitable for removal by this method

Severe haemorrhage is more easily controlled and difficulties resulting from infiltration of the lateral ligaments deep in the pelvis or fixity anteriorly are lessened

This position is essential for the performance of an abdomino anal resection where the anastomosis is performed from the perineum after the bowel has been extruded through the anal orifice and also allows irrigation of the lumen of the rectum when a restorative operation is contemplated

Sigmoidoscopy may be carried out whilst the abdomen is open this being particularly useful in the presence of a soft villous tumour whose limits it is impossible to define by palpation from above The employment of the synchronous or two team combined excision has been one of the major factors responsible for the high operability (resectability) rate achieved

Post operative difficulties of micturition are more frequent following this operation than after perineo abdominal excision This is probably due to a more extensive removal of pelvic tissues with the increased risk of injury to the nervi erigentes

*Perineal and anterior excisions*—Both these operations have a limited place in the treatment of carcinoma of the rectum A two stage perineal excision with a preliminary colostomy (Lockhart Mummery 1907) may be used as a palliative measure for a growth situated low in the rectum in a poor risk patient Anterior excision (Hartmann 1923) for growths in the upper two thirds of the rectum or rectosigmoid may be extended downwards so that the bowel is divided from the abdomen at the junction of the rectum and anus Such a procedure is justifiable in a patient whose general state is poor since it avoids the additional perineal phase of combined excision

*Pelvic evisceration*—Pelvic evisceration is justifiable only when the main extension of the growth is in an anterior direction and there is little or no lateral spread If there be lateral spread the risk of local recurrence makes this operation unjustifiable The poor prognosis associated with growths of high malignancy is also a contra indication The ideal case is one in which the growth has spread directly into the bladder with little or no extension in any other direction

*Restorative resection*—In certain selected cases removal of a carcinoma of the rectum with restoration of continuity of the bowel has a place in the treatment of growths in this region The infrequency of downward lymphatic spread or of lateral spread when a growth is situated above the level of the peritoneal reflection has already been discussed

Certain criteria are necessary for the performance of such operations

(1) The operation must allow of normal defaecation It is therefore necessary to preserve the anal canal with its lining and musculature and also a portion of the rectal wall lying above the ano rectal ring The rectum and meso rectum must be removed *en bloc* for a distance of at least 5 centimetres—by measurement—below the lower edge of the growth and the procedure should include excision of the same upward lymphatic field as that required for radical combined excision (Fig 116) Anterior resection and abdomino anal resection (Maunsell Weir) both fulfil these requirements The latter operation however is not often performed since it requires an extra long loop of sigmoid colon and further the functional result is not always perfect

Proctosigmoidectomy and operations of the pull through type often give poor control and are not recommended in the treatment of cancer of the rectum

be used for anastomosis There has been a marked fall in the number of recurrences since using this method (Table I)

The bowel lumen and divided ends are cleansed in a similar manner during resection of a carcinoma of the colon even though the bowel above and below the growth has been excluded as suggested by Warren Cole

*Operability (resectability) rate*

Owing to the distressing terminal symptoms produced by a rectal carcinoma every effort should be made to remove completely the primary lesion In fact removal of the growth is the only satisfactory method of palliative treatment For this reason it will be seen that the operability (resectability) rate is found to be high in the series of cases reported (Table II)

TABLE II

OPERABILITY (RESECTABILITY) RATE FOR CARCINOMA OF THE RECTUM AND RECTO SIGMOID (1948 1956)

| *Patients seen* | *Refused operation or for diagnosis only* | *Inoperable* | *Resected or excised* | *Operability rate (per cent)* |
|---|---|---|---|---|
| 642 | 13 | 33 | 596 | 94 8 |

Colostomy alone has little place in the palliative treatment of carcinoma of the rectum and is indicated only in the presence of obstruction or when there is excessive rectal discharge produced by secondary infection of the growth In the large majority of cases exploratory laparotomy is essential in order to decide operability the degree of local spread and the presence of distant metastases Even then inspection and palpation of the primary growth may not allow complete assessment of the extent of local spread It therefore may be necessary to perform a trial dissection on the fixed aspects of the tumour Inflammatory or malignant infiltration may then be differentiated

In the series of cases recorded no fewer than 75 per cent of the patients with inoperable growths were explored before this decision was definitely made

Metastasis in the liver is not necessarily a contra indication to extirpation of the primary growth since such patients may survive for several years and die in comparative comfort following palliative removal of the growth When it is estimated that not more than one half of the liver is replaced by growth palliative amputation or resection of the primary tumour should be performed provided that it is locally removable

Excision of a solitary hepatic metastasis may also be worth while especially if it is situated in the left lobe of the liver

It may be difficult to decide with certainty the nature of a small hepatic nodule of less than 2 centimetres in diameter but the majority of typical liver secondaries will prove to be malignant in the presence of a primary carcinoma in the large intestine If there be any doubt as to the nature of a nodule in the liver the most radical operation for the primary growth should be performed whereas a less radical procedure may be considered adequate if the nodule is undoubtedly

*Transplantation of free malignant cells* —It has long been known when the large intestine is the site of a carcinoma that the mucous membrane of this portion of the bowel exhibits areas of increased activity The large intestine is in fact one of the commonest sites for multiple primary tumours Dukes (1952) found that multiple growths occurred in 2 9 per cent and Gabriel (1948) reported an incidence of 4 7 per cent Morgan (1955) found multiple growths in 3 per cent of 102 specimens removed by anterior resection

It is not surprising therefore to find that malignant cells may be implanted during operations for carcinoma of the colon or rectum Such implantation was noted at St Mark s Hospital some 20 years ago when recurrence at the suture line was found in one of the author s cases following an anterior resection Free malignant cells from a carcinoma of the large intestine may also become implanted into an anal operation wound

The risk of implantation however was not fully realized until Morgan and Lloyd Davies (1950) reported the results of their first series of restorative operations Morgan s personal recurrence rate in 14 cases of this series was disturbingly high—3 in 14 (21 4 per cent) (Table I)

TABLE I

RELATIONSHIP OF SUTURE LINE RECURRENCES AND MERCURIC WASH OUT

| | *No wash out* | *Wash out* |
|---|---|---|
| Number of cases | 14 | 136 |
| Number of outer line recurrences | 3 | 2 |
| Percentage | 21 4 | 1 5 |

Goligher et al (1951) have shown that transplantation of growth probably accounted for about 50 per cent of the recurrences at or near the suture line in specimens examined at St Mark s Hospital Vink (1954) demonstrated the ease of transplantation of the Brown Pearce tumour in the rabbit into a colonic suture line in the same species This investigation also indicated that disinfection of the large intestine by Sulfasuxidine and streptomycin may increase the chances of transplantation of free malignant cells

Free malignant cells were demonstrated in the lumen of the colon in 42 per cent of the proximal ends and 65 per cent of the distal ends of resected portions of colon for average distances of 21 and 10 centimetres respectively by McGrew et al (1954) Exclusion of the portion of the bowel to be resected is therefore advisable before mobilization of the colon is commenced

Since 1948 at St Mark s Hospital we have aimed at the destruction of these free intraluminar malignant cells by irrigation of the bowel lumen with 1 500 mercury perchloride When performing restorative resection for a carcinoma of the lower sigmoid rectosigmoid or intraperitoneal rectum the intestine below the growth is excluded by a suitable clamp The distal bowel is then thoroughly irrigated through the anus excess fluid removed and the rectum dried The bowel is then divided distal to the exclusion clamp Further after division of the proximal colon its lumen also is swabbed thoroughly with the same solution paying attention to the cut end of the bowel Under no circumstances should crushed bowel

be used for anastomosis There has been a marked fall in the number of recurrences since using this method (Table I)

The bowel lumen and divided ends are cleansed in a similar manner during resection of a carcinoma of the colon even though the bowel above and below the growth has been excluded as suggested by Warren Cole

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malignant in nature Biopsy of the liver nodule and a frozen section are of value in doubtful cases

Left hepatic lobectomy for a solitary secondary deposit in the left lobe of the liver has been performed in 2 patients One patient who survived 5 years following an abdomino-perineal excision lived for an additional 4 years after left hepatic lobectomy The other patient is still alive and well 5½ years after combined excision and left hepatic lobectomy performed at the same operation (Fig 117)

Radical operations were carried out in 80 per cent of the patients treated by either synchronous combined excision or restorative anterior resection The proportion

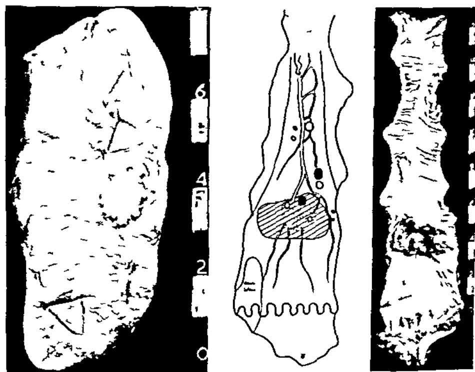


FIG 117—Carcinoma of the rectum removed by combined excision Left, hepatic lobectomy performed at the same operation

of growths found suitable for treatment by a restorative operation was 27 per cent (Table III) The site of primary tumours in 138 restorative anterior resections will be seen in Table IV

TABLE III

CARCINOMA OF THE RECTUM—PROPORTION OF RESTORATIVE OPERATIONS

(Personal series 1948–1956)

| | | |
|---|---|---|
| Total major operations | | 523 |
| Total restorative resections | Anterior | 138 |
| | Abdomino-anal | 4 |
| | | 142 (27 per cent) |

The fact that the cases recorded were unselected is shown in Table V.

TABLE IV

SITE OF PRIMARY CARCINOMA IN 138 RESTORATIVE ANTERIOR RESECTIONS

| | Cases | Percentage |
|---|---|---|
| Supra peritoneal rectum (upper third) | 73 | 57·9 |
| Recto-sigmoid | 57 | 41·3 |
| Multiple sites | 5 | 3·6 |
| Middle third rectum (partly above and below peritoneal reflection) | 3 | 2·2 |

TABLE V

COMPARATIVE CLASSIFICATION OF EXTENT OF GROWTHS

| St Mark's Hospital general series (per cent) | Personal series (per cent) |
|---|---|
| A 14·5 | A 16·1 |
| B 35 | B 33·5 |
| C 50·5 | C 50·4 |

*Mortality rate*

The mortality rate for 523 major operations for cancer of the rectum and rectosigmoid is shown in Table VI. The mortality rate for synchronous combined excision and for restorative anterior resection were the same—4·2 per cent

TABLE VI

MORTALITY RATE—523 OPERATIONS FOR CARCINOMA OF RECTUM AND RECTOSIGMOID

(Personal series 1948–1956)

| | Number | Deaths | Mortality rate (per cent) |
|---|---|---|---|
| *Non-restorative operations* | | | |
| Synchronous combined excision | 361 | 14 | 3·9 |
| Hartmann's operation (anterior excision) | 11 | 1 | |
| Perineal excision | 1 | — | — |
| Perineo-abdominal excision | 1 | — | — |
| Abdomino-perineal excision | 5 | — | — |
| Pelvic clearance | 1 | — | — |
| Total procto-colectomy | 1 | 1 | |
| | 381 | 16 | 4·2 |
| *Restorative operation* | | | |
| (Post mercuric washout) | | | |
| Abdomino anal excision | 4 | — | — |
| Anterior resection | 138 | 6 | 4·3 |
| | 142 | 6 | 4·2 |

*Survival rate*

The survival rates following synchronous combined and restorative anterior excision for both radical operations and palliative operations are shown in Table VII These figures would appear to indicate that the survival rate following radical restorative anterior resection was better than that achieved by radical synchronous combined excision This is a fallacious deduction since those growths removed by anterior resection were carefully selected This selection of cases treated by anterior resection is shown in Table VIII It will be seen that twice as many early or A growths of the intraperitoneal rectum or rectosigmoid were removed by anterior resection than by combined excision

*It is difficult to obtain a true* comparison of the results of treatment of carcinoma of the upper rectum and rectosigmoid by combined excision and by restorative resection This can only be attained by comparing the results of treatment of *growths at the same site of the same extent and of similar age and sex distribution*

The crude 5 year survival rate for the personal series of 110 *radical* restorative resections is 66 per cent When *corrected for deaths due to intercurrent diseases* the survival rate is 81 per cent The similarly corrected survival rate of a comparable group of growths removed by combined excision was 78 5 per cent

It is not claimed that this slight difference *is of statistical significance* but it does at any rate support the contention that restorative resection has a place in the treatment of suitable malignant growths of the upper rectum and rectosigmoid and

TABLE VII

SYNCHRONOUS COMBINED EXCISION AND RESTORATIVE ANTERIOR RESECTION—5-YEAR SURVIVAL RATES

(Personal series 1948–1956)

| | *Radical operation (per cent)* | *Palliative operation (per cent)* | *Total cases (per cent)* |
|---|---|---|---|
| *Synchronous combined excision* | 55 9 | 6 6 | 46 |
| Restorative anterior resection | 66 1 | 10 6 | 54 |

TABLE VIII

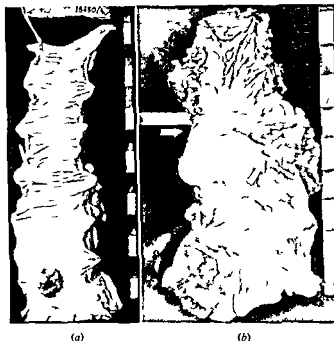
COMPARISON OF PROPORTION OF A B AND C CASES IN OPERATIONS FOR GROWTHS OF THE UPPER RECTUM AND RECTOSIGMOID

(Personal series 1948–1956)

| *Operations* | *No of cases* | *A (per cent)* | *B (per cent)* | *C (per cent)* |
|---|---|---|---|---|
| Combined excisions | 109 | 9 8 | 36 6 | 53 6 |
| Anterior resections | 138 | 21 2 | 35 6 | 43 2 |

that patients treated in this way have as good a prognosis as those treated by other radical operations

*Effect of high ligation* —The effect upon the 5 year survival rate of high ligation of the inferior mesenteric artery at its origin has yet to be revealed High ligation of this vessel has been carried out on 145 occasions for growths of the rectum and left colon with one death which could have been avoided The ligation was performed in 118 excisions or resections for carcinoma of the rectum and rectosigmoid



(*a*) (*b*)

FIG 118 —(*a*) Specimen removed by restorative anterior resection (*b*) A second primary carcinoma developing below the suture line (Specimen removed by combined excision )

The number of C2 cases (a malignant lymph node immediately below the point of ligation of the inferior mesenteric artery) in these 118 specimens was 9 (7 6 per cent)

At St Mark s Hospital an analysis of 1 000 specimens following combined excision of the rectum without high ligation of the main vessels shows that the incidence of C2 cases was 138 (13 8 per cent) It would appear therefore—though the series of high ligations is so far not large—that the number of C2 cases has been approximately halved by this procedure

The 5 year survival rate for carcinoma of the rectum with lymphatic metastasis treated by combined excision even though there be an unaffected lymph node between the point of ligation of the main vessel and the highest malignant gland removed (Dukes classification C1) is only 30 per cent Statistical evidence suggests that following high ligation of the inferior mesenteric artery at combined excision of the rectum improvement of the 5 year survival rate might be in the region of 3 per cent

*Follow up*

Since a greater amount of large intestine is retained following a restorative resection *it is essential that the patient should be carefully followed up* The suture line may easily be inspected by sigmoidoscopy which should be carried out at regular intervals In addition an annual barium enema x ray examination is also advisable to exclude a second primary growth

The importance of careful follow up is illustrated in Fig 118 where a primary tumour was found developing below the suture line 3 years after anterior resection This patient was submitted to combined excision and colostomy

## MALIGNANT ADENOMAS

The discovery of a small carcinoma in an apparently innocent adenoma after its removal is often a problem to the surgeon

**Carcinoma *in situ***

When histological examination of an adenoma reveals a focus of carcinoma *in situ* with no invasion provided that a fringe of normal mucosa or pedicle has been removed apart from careful follow up no further treatment is necessary

***Invasive carcinoma***

Provided that the pedicle of a pedunculated adenoma is found free of malignancy or there is an adequate free margin of normal tissue on careful histological ex amination no further treatment is necessary as long as the lesion be situated low enough for future inspection *both* by palpation and by sigmoidoscopy

A patient with an invasive carcinoma in a sessile adenoma or involvement of the stalk of a pedunculated adenoma situated beyond the easy reach of the finger should be subjected to radical surgery

A small malignant adenoma situated low in the rectum the site of which can be inspected easily and thoroughly both by palpation and by endoscopy may be removed by diathermy and the site of operation fulgurated Regular observa tion is necessary and any recurrence should always be treated by radical surgery

*Whatever the site or size of an adenoma undergoing malignant change* if the growth is of high grade malignancy radical surgical extirpation should be carried out

In a series of 2 500 specimens of carcinoma of the rectum at St Mark s Hospital 47 (1 9 per cent) were removed by local excision and follow up of these cases indicates that treatment has been satisfactory

## CARCINOMA OF THE LEFT COLON

**Operative mortality rate**

The operative mortality rate of resection of the left colon for carcinoma has in the past been higher than for resection of the right and transverse portions of the large intestine Though in recent years there has been a marked fall in the mortality *rate for resection of growths of all portions of the colon* the mortality rate follow ing resection of the left colon is still approximately twice that of resection of the right colon At St Bartholomew s Hospital London in the years 1930–1936 the

operative mortality rate following resection of carcinomas of the right and trans verse colon was 12 per cent and during the same period that for resection of the left colon including the splenic flexure was 24 per cent In the years 1947–1950 at the same hospital the mortality rate for resection of the right colon had fallen to 3 per cent and that of the left colon including the splenic flexure to 7 per cent

At St Mark s Hospital the operative mortality rate for resection of the left colon between 1928 and 1942 was 14 9 per cent in 87 operations whereas between the years 1943 and 1955 the mortality rate had halved 7 4 per cent in 244 opera tions The operative mortality rate for carcinoma of the right colon during this latter period was 4 per cent This marked fall in mortality rate was achieved in spite of an increase in the operability (resectability) rate

Extraperitoneal colectomy or the Paul Mikulicz operation has been performed in the past owing to its lower operative mortality rate though resection and anasto mosis is a more radical procedure At St Mark s Hospital (1945–1950) it is interest ing to note that the mortality rate for resection and anastomosis for carcinoma of the sigmoid colon compared favourably with that of extraperitoneal colectomy the operative mortality rates being 3 7 and 3 per cent respectively Open anasto mosis following resection has replaced the closed technique and one stage opera tions are usually employed

These improved results are due to a better appreciation of the physiology of a patient suffering from malignant disease of the gastro intestinal tract especially when complicated by obstruction The importance of preparation and post operative care especially with regard to fluid and electrolyte balance the correc tion of hypoproteinaemia and anaemia the control of infection and the need for adequate vitamin concentration are now all fully realized Advances in anaesthesia in addition to diminishing chest complications have made prolonged operations requiring wide mobilization of mesenteries much safer Earlier clinical diagnosis and progress in radiological technique are also factors making for better prognosis

The higher operative mortality rate for resection of the left colon as compared with the right though due partly to the different functions and the type of faecal content of these portions of the colon has hitherto been considered due mainly to the poorer blood supply on the left side This has often resulted in a more restricted removal of the mesenteric lymphatic field of the left colon

The incidence of metastasis in lymphatic nodes at the origin of the inferior mesenteric artery was found by Grinnell (1953) to be 17 per cent McElwain et al (1954) reported that in 90 resections for carcinoma of the left colon 12 (13 3 per cent) had a malignant node near the origin of the inferior mesenteric artery In 9 per cent of these specimens ligation below the left colic artery would have failed to remove these nodes

Ligation of the inferior mesenteric artery at its origin would appear to be essen tial for the radical treatment of carcinoma of the left colon

## SURVIVAL RATE

In a comprehensive review on the results of treatment of carcinoma of the colon and rectum Grinnell (1953) found that the survival rates for carcinoma of the right and left portions of the colon showed little difference the survival rate for the right colon being 54 5 per cent and that for the left colon 55 7 per cent In a

*Follow up*

Since a greater amount of large intestine is retained following a restorative resection it is essential that the patient should be carefully followed up The suture *line may easily be inspected by sigmoidoscopy which should be carried out at* regular intervals In addition an annual barium enema x ray examination is also advisable to exclude a second primary growth

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TABLE X
OPERABILITY RATE FOR ALL CASES OF CARCINOMA OF THE COLON
(St Mark s Hospital)

| *Years* | *No of cases* | *Growth removed (per cent)* | *Growth not removed (per cent)* |
|---|---|---|---|
| 1935–1944 | 209 | 65 0 | 35 0 |
| 1945–1950 | 249 | 91 5 | 8 5 |

TABLE XI
RISE IN PROPORTION OF RADICAL EXCISIONS FOR CARCINOMA OF THE COLON
(St Mark s Hospital)

| *Years* | *No of cases* | *Inoperable (per cent)* | *Palliative excision (per cent)* | *Radical excision (per cent)* |
|---|---|---|---|---|
| 1935 1944 | 209 | 35 0 | 7 0 | 58 0 |
| 1945–1950 | 249 | 8 5 ( – 26 0) | 20 0 ( + 13 0) | 71 8 ( + 13 0) |

TABLE XII
TYPES OF OPERATION FOR CARCINOMA OF THE SIGMOID AND RECTOSIGMOID
(St Mark s Hospital)

| *Years* | *No of cases* | *Non restorative radical excisions (per cent)* | *Restorative resections (per cent)* |
|---|---|---|---|
| 1935–1944 | 136 | 61 6 | 38 4 |
| 1945 1950 | 228 | 39 6 | 60 4 |

## THE BLOOD SUPPLY OF THE LEFT COLON AND RECTUM

(High ligation of the inferior mesenteric artery)

Ligation of the inferior mesenteric artery was considered as long ago as 1908 by Archibald and by Moynihan as a means of removing the greatest possible mesenteric field in operations for carcinoma of the rectum and left colon More recently Ault et al (1952) Grinnell and Hiatt (1952) and Goligher (1954) have investigated the blood supply of this portion of the large intestine There appears however to be some confusion in nomenclature and Griffiths (1956) has re investigated the anatomy of the blood supply This study was carried out by means of both post mortem arterial injection and aortography so that the vascular pattern was seen without disturbing in any way the anatomical position of the large intestine in 100 subjects

It has been observed at operation before mobilization of the colon and confirmed by Griffiths (1956) that in some 89 per cent of subjects the left colic artery

small series of growths of the hepatic flexure the survival rate was surprisingly low—namely 25 per cent or less than 50 per cent that for the remainder of the colon This is due probably to the fact that owing to its location the carcinoma readily invades the region of the duodenum and liver

In spite of the fact that as a rule in the past a wider removal of the mesentery has generally been accomplished for growths of the right colon than for those of the left side the 3 year survival rates following operations for 108 carcinomas of the colon at St Bartholomew s Hospital since 1948 showed that the survival rate for carcinoma of the right colon is lower than for growths of the left side (Table IX)

TABLE IX
3 YEAR SURVIVAL RATE FOR CARCINOMA OF THE COLON

| *Site* | *Number of cases* | *Number of 3 year survivals* | *Survival rate percentage* |
|---|---|---|---|
| Right colon including *section transverse* | 52 | 33 | 63 |
| Left colon | 56 | 40 | 71 |

The 5 year survival rate in a smaller series was 50 per cent for the right side and 59 per cent for the left colon

There has been little change in the 5 year survival rate following operations for carcinoma of the left colon in recent years At St Mark s Hospital the 5 year survival rate between 1928 and 1942 was 59 4 per cent and that from 1943 to 1952 56 9 per cent

A *more radical operation for carcinoma of the right colon is* hardly possible and time will tell whether a more radical removal of the lymphatic field on the left side made possible by high ligation of the inferior mesenteric artery at its origin from the aorta will improve the results of treatment of carcinoma of this region of the colon

Between 1928 and 1951 at St Mark s Hospital before high ligation of the inferior mesenteric artery was practised for carcinoma of the left colon the 5 year *survival rate for growths of the left colon which had spread to the lymphatic* nodes was 35 4 per cent However there was little difference between the 5 year survival rate in those cases in which there was a lymph node free from metastasis below the site of ligation of the main vessels (C1) and those in which a metastatic node was found up to this site (C2) The 5 year survival rate was 36 6 per cent for C1 cases and 33 3 per cent for C2 cases

**Operability (resectability) rate**

In recent years there has been a 26 per cent increase in the operability rate for carcinoma of the colon as shown in Table X From further analysis of these figures it will be seen that the higher operability rate has resulted in an equal increase of 13 per cent in both radical and palliative operations (Table XI)

In addition to the higher operability rate the number of restorative procedures employed for the treatment of carcinoma of the rectosigmoid and sigmoid colon—during the same period—show a marked increase (Table XII)

after looping slightly downwards from its origin from the inferior mesenteric artery ascends directly upwards and outwards towards the splenic flexure where it divides into two main branches some 2 inches from the intestine This vessel does *not* pass more or less transversely outwards to the descending colon as often depicted in anatomical illustrations In fact the left colic artery soon after its origin runs upwards almost parallel with the aorta (Figs 119 and 120) It is in close relationship to the inferior mesenteric vein as this vessel runs upwards to the paraduodenal fold The vein lies close to the outer side of the left colic artery before it passes underneath the artery The left colic artery may give off a transverse or lower left colic branch which does pass transversely to the descending colon in 25 per cent of subjects

The marginal artery described by von Haller (1786) and Drummond (1914) is the vessel from which the vasa recti arise In the right and transverse portions of the colon the marginal artery is formed by the arcades of the main vessels whereas in the left colon there is a distinct marginal artery placed about 1–1½ inches from the mesenteric border of the colon It is difficult to find in obese subjects The marginal artery was found to be constant and well developed in all the 100 specimens

The critical point in the distal sigmoid mesentery described by Sudeck (1907) was not found but there was a definite critical point in the region of the splenic flexure In this region the marginal vessel between the two terminal branches of the left colic artery was usually very small and in order to enable blood from the superior mesenteric artery via its middle colic or right colic branch to supply the left colon the preservation of this bifurcation of the left colic artery is essential

The sigmoid branches of the inferior mesenteric artery lie entirely in the mesosigmoid mesentery in which situation the marginal artery is well developed Generally there is no need to preserve the bifurcation of the sigmoid vessels but should the first sigmoid artery bifurcate near the medial border of the colon for additional safety it is wise to preserve this division

The middle colic artery was found to be absent in 22 per cent of the subjects examined and in such cases the right colic joined the marginal artery near the hepatic flexure An anastomosis between the left and middle colic arteries was also found in 10 per cent of subjects at the root of the mesocolon though at operation owing to its position this vessel is seldom seen

Following high ligation of the inferior mesenteric artery the anastomosis between the superior rectal artery and branches of the middle rectal artery is usually capable of supplying blood to the whole sigmoid colon

The points of surgical importance resulting from this investigation are briefly

(1) Removal of a wide area of colonic mesentery after high ligation of the inferior mesenteric artery requires in addition ligation of the left colic artery and the inferior mesenteric vein When this has been carried out it is essential to preserve the bifurcation of the left colic artery in the region of the splenic flexure

(2) The position and presence of the middle colic artery should be verified before a temporary proximal transverse colostomy is established since when the latter artery is absent the marginal vessel may be readily damaged High ligation of the inferior mesenteric artery under such circumstances may not permit a satisfactory blood supply to the left colon A temporary transverse colostomy should be placed as near the hepatic flexure as possible in order to avoid injury to the left branch of the middle colic artery

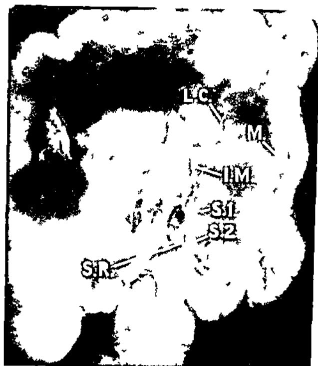
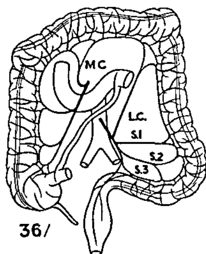



FIG 119.—Radiograph of autopsy specimen injected with radio opaque material showing distribution of the inferior mesenteric artery (*By courtesy of the Editor of* Ann R Coll Surg Engl)



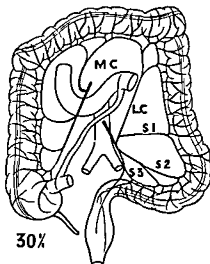




FIG 120.—Diagrams showing the two variations of the common pattern of distribution of the inferior mesenteric artery M C—Middle colic artery L C—Left colic artery S—Sigmoid artery (*By courtesy of the Editor of* Ann R Coll Surg Engl)

# CHAPTER 21

# ADVANCES IN THE RADIOLOGY OF THE BILIARY TRACT

D H CUMMACK

RADIOLOGY plays an increasingly important part in the investigation of disease of the biliary tract and provides as high a degree of diagnostic accuracy as in any other system in the body

One or more of the following radiological procedures may be employed in the investigation of the biliary tract

## PLAIN RADIOGRAPHY

Plain radiography is of limited value but is an essential preliminary investigation

### Normal findings

The ducts are never visualized and only very occasionally can the normal gall bladder be identified as a faint shadow A gall bladder shadow of moderate density due to an increase of calcium in the bile is occasionally seen This does not signify disease of the biliary tract and the term limy bile should be restricted to this condition

### Abnormal findings

*Gall stones* —Calcified gall stones single or multiple may be seen Unless the stones have a typical peripheral ring of calcium it is not possible to give a definite diagnosis on the plain film alone Calcified costal cartilages tuberculosis of the right kidney or suprarenal gland renal calculi calcified glands calcification in the pancreas and opacities in the bowel are the commonest causes of difficulty in diagnosis Oblique or stereoscopic views may help but in doubtful cases chole cystography is indicated

It has been stated that only 10 per cent of gall stones are visible on the plain film (Shanks and Kerley 1950) but this figure is probably on the low side In 60 of a personal series of 138 cases—that is 43 per cent—the gall stones were calcified and had been noted on the plain film before operation Rarely a gall stone is iden tified by the presence of stellate areas of translucency due to gas filled clefts within it Even more rarely cholesterol stones may be shown as rounded areas of trans lucency due to the fact that cholesterol like fat is less radio opaque than the other soft tissues of the body

Calcified sludge in the gall bladder gives an irregular granular appearance being most obvious in the erect position as it sinks to the fundus It must not be mistaken for limy bile Calcified sludge may also be noted in the ducts

*Calcified gall bladder* —In some cases of chronic cholecystitis the gall bladder wall contains plaques of calcification the so called porcelain gall bladder This presents little difficulty in diagnosis except sometimes for differentiation from a large calcified stone in the gall bladder

(3) Only when the first sigmoid artery divides near the border of the intestine need its bifurcation be preserved

(4) The marginal artery and the vasa recti must be carefully preserved right up to the proposed division of the bowel In 145 high ligations one operation in an obese patient ended fatally owing to misjudgment of the site of ligation of the marginal artery in relation to the divided end of the bowel It is unwise to perform a high ligation of the inferior mesenteric vessel in an obese subject when the anatomy cannot be verified In the presence of gross arteriosclerosis high ligation of the inferior mesenteric artery is also to be avoided

For radical extirpation of a carcinoma at the splenic flexure in the descending or sigmoid colon ligation of the inferior mesenteric artery at its origin is desirable When this has been carried out in order to restore continuity without tension and with the certainty of a good blood supply wide mobilization of the left and maybe the transverse colon is necessary

Although arterial pulsation and colour and temperature changes in the intestine are indications of the state of its arterial supply the only sure evidence of its viability is arterial bleeding from the divided ends of the bowel

ACKNOWLEDGEMENT

I am indebted to the Research Department and particularly to H J R Bussey of St Mark s Hospital and to the Statistical Department at St Bartholomew s Hospital for the assistance so readily afforded me in the preparation of this chapter

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# ORAL CHOLECYSTOGRAPHY

Oral cholecystography is the most important method of investigation and has the great merit of being simple and safe Telepaque (3 (3 amino—2 4 6—tri iodophenyl) —2—ethyl propanoic acid) has now largely superseded pheniodol as it is now generally recognized that it produces a denser shadow and has fewer unpleasant side effects The diagnostic accuracy of the investigation is not affected by lactation as the amount of Telepaque excreted in the milk is small (Holmdal 1956) Age is no contra indication the medium being well tolerated by children and the aged Six tablets (3 grammes) of Telepaque is the usual dose for adults but in the obese this can be increased to 12 tablets Following preparation with laxatives Telepaque is taken in the evening after a meal which should contain fat Films are taken after approximately 12-14 hours the patient having had nothing to eat or drink in the interval It is most desirable that the patient be screened and serial films taken with compression and graduated rotation so that several pairs can be viewed stereoscopically (Cummack 1952) It is essential to take films in both the erect and supine positions otherwise many stones especially of the floating type will be missed The films must be checked by the radiologist at the time of the examination

Various modifications have been recommended for example fractional dosage tomography of gall bladder and so on but in the author s opinion these are unnecessary

It is not proposed to describe the normal appearances or congenital abnormalities in this section except to indicate that occasionally the ducts are faintly opacified even without a fatty meal The degree of opacification however is seldom sufficient to exclude disease or abnormalities of the ducts and for adequate visualization of these further investigation is required

In many centres the examination is completed by a fatty meal and subsequent films It is claimed that this may show calculi not seen on initial films the outline of the cystic duct and bile duct and sometimes hepatic ducts and the ability of the gall bladder to contract

Very few calculi are missed if the technique previously described is used and the ducts are more clearly and consistently shown by the intravenous method Furthermore it seems reasonable that if the gall bladder fills with opaque medium it must previously have contracted and emptied A fatty meal is therefore superfluous and should be given only if the dubious entity of biliary dyskinesia is suspected

For descriptive purposes the gall bladder is classified as showing (1) good or normal concentration (2) poor concentration or (3) no concentration

The distinction between good and poor concentration must be a personal one but in general there is little difficulty in arriving at a decision A normally concentrating gall bladder casts a dense shadow while the shadow of the poorly concentrating gall bladder at most is only slightly more dense than the liver shadow

**The normally concentrating gall bladder**

If the gall bladder concentrates well and shows no calculi nor other abnormality one presumes that it is likely to be normal This cannot be completely accurate and in fact Gordon (1953) stated that disease may be present in 20 per cent of normally concentrating gall bladders In approximately one-quarter of this 20 per

*Gas in the biliary tract*—This is a most important observation The gas is variable in extent and in some cases occurs intermittently When present in the intrahepatic ducts the clear branching translucencies within the liver shadow cannot be mistaken for anything else (Fig 121) Difficulty in interpretation occurs when only the common bile duct and perhaps the common hepatic duct are filled with gas The differentiation from gas in the duodenum or colon is then by no means easy

Gas is always present when there is a functioning cholecyst enterostomy or choledoch enterostomy and also when there is a fistula between the gall bladder and the bowel (Figs 121 and 122) It may also result from incompetence of the sphincter of Oddi following passage of a stone after sphincterotomy or from distortion by carcinoma or peptic ulcer of the second part of the duodenum Rarely it is due to infection with gas forming organisms



FIG 121 —Gas in the biliary tract due to a fistula between the gall bladder and the colon



FIG 122 —Same case as illustrated in Fig 121 showing the fistula outlined by barium enema

Gas may be present in the biliary tract in any intestinal obstruction and is most commonly seen in gall stone ileus In these cases the gas is due mainly to the fistula When there is no fistula it is presumed that the increased intraduodenal pressure forces gas through the ampulla of Vater up the common bile duct

*Empyema of the gall bladder*—The patient s condition rarely justifies any investigation other than plain radiography The films may show a soft tissue shadow due to the enlarged gall bladder A careful search should be made for gall stones

concentration and was subsequently removed disease was found in 40 cases that is approximately 90 per cent Stones had been previously diagnosed radiologically in 33 cases (75 per cent) and in 3 more cases a few small calculi were found at operation

**The non concentrating gall bladder**

Failure of the gall bladder to concentrate suggests that it is pathological The accuracy of this has been stated to be approximately 70–97 per cent as with the poorly concentrating gall bladder In the author s series of 68 cases the presence of disease was confirmed in 60 (just under 90 per cent) Occasionally the ducts are faintly opacified without a fatty meal Non concentration or poor concentration in these cases is proof that the gall bladder is diseased as the medium has obviously been absorbed and excreted

It is convenient to discuss both the non-concentrating and the poorly concentrating gall bladders together as the causes of misleading appearances are the same in both

The causes of poor or absent gall bladder shadows when in fact the gall bladder is normal are as follows

(1) Failure of absorption from vomiting diarrhoea gastric stasis and in the malabsorption syndrome The mild diarrhoea caused by Telepaque and pheniodol does not interfere with absorption

(2) Impairment of the excretory function of the liver for example cirrhosis amoebiasis metastases and hepatitis

(3) Biliary stasis from obstruction

In most cases the cause of the impaired concentration can be inferred from the clinical or biochemical findings for example jaundice vomiting or diarrhoea In doubtful cases further information can be obtained from intravenous chole cystography

**Biliary dyskinesia**

Biliary dyskinesia is stated to be due to a disturbance of the neuromuscular mechanism of the gall bladder and the sphincter of Oddi Articles on this subject (Copleman 1946 Ivy 1947 Feldman 1948 and Shanks and Kerley 1950) are most conflicting

Two types are described (1) spastic distension due to vagal over activity and (2) atonic distension due to sympathetic over activity

The radiological features of this condition are dilatation of the ducts and some times the gall bladder with reflux into the hepatic ducts following a fatty meal In addition the passage of the medium into the duodenum is delayed

There is no doubt that many cases of calculi in the ducts chronic pancreatitis and stricture at the lower end of the common bile duct were labelled biliary dyskinesia in the past Before a diagnosis of biliary dyskinesia can be considered all other lesions of the biliary tract must be excluded In practice the diagnosis need rarely be made

## INTRAVENOUS CHOLECYSTOGRAPHY AND CHOLANGIOGRAPHY (CHOLECYSTANGIOGRAPHY)

This technique introduced by Frommhold (1953 a and b) in Germany constitutes a major advance in the radiological diagnosis of biliary disease Biligrafin the

cent however gall stones are present In addition Gordon includes in this 20 per cent cases of cholesterolosis a condition of doubtful clinical importance Thus a normally concentrating gall bladder without calculi excludes disease in approximately 90 per cent of cases Phrygian cap deformity and septa in the gall bladder are not considered in themselves to have any real significance

Calculi are the most common abnormality noted in the normally concentrating gall bladder They usually sink to the fundus in the erect position but occasionally form a layer in the middle of the gall bladder—so called floating gall stones The beaded appearance of the cystic duct due to Heister s valves must not be mistaken for non opaque stones A polyp in the gall bladder is occasionally seen and is easily recognized as a small smooth fixed translucency adjoining the wall Rokitansky Aschoff sinuses cause a typical shaggy double contour of the gall bladder wall (Fig 123) When marked they may be difficult to distinguish from



FIG 123 —Rokitansky Aschoff sinuses Film 14 hours after Telepaque

*multiple* small non opaque gall stones The condition has been called chole cystitis glandularis intramural diverticulosis and adenomyoma but opinions differ as to its nature and significance

**The poorly concentrating gall bladder**

Poor concentration by the gall bladder usually indicates that it is pathological The accuracy of this observation has been variously estimated between 70 and 97 per cent In a personal series of 44 cases *where the gall bladder showed poor*

position with an over-couch tube in the usual manner The films should be checked by the radiologist before the patient is dismissed A fatty meal is rarely necessary

Aldridge (1955) has described a rapid method of examination of the biliary tract He recommends a fatty meal to empty the gall bladder followed 1½ hours later by an intravenous injection of pethidine hydrochloride to contract the sphincter of Oddi Biligrafin is injected immediately afterwards This is an ingenious technique but it has little advantage over the method already described and demands careful supervision which may be difficult in a busy department

### Normal appearances with Biligrafin alone

After 20–30 minutes the hepatic duct and common bile duct and usually the cystic duct are clearly seen and some of the medium may have reached the gall bladder and the duodenum The calibre of the ducts varies from case to case but should not normally exceed 8 millimetres Usually the lower end of the common bile duct tapers gradually to a point If the lower end is not clearly seen this must not be considered abnormal and further films should be taken Between ½ and 2 hours after injection the gall bladder gradually fills with opaque medium In the erect position a thick clear band is seen between two opacified zones—the layer or stratification effect (Fig 124) This clear layer is caused by the pre existing bile and mucus in the gall bladder and may be 1 or more centimetres in thickness A dense rim of medium is occasionally seen peripherally in the fundus of the gall bladder due to active concentration by its wall Later films show increasing concentration of the medium in the gall bladder Care must be taken not to mistake the filled duodenal bulb for the gall bladder After 2 hours the common bile duct is still moderately clearly seen Sometimes a pyelogram is obtained but this should cause no confusion provided this possibility is borne in mind

### Normal appearances with previous administration of Telepaque

The stratification effect in the erect position is again present but is less obvious since the lower two thirds or three quarters of the gall bladder are already opacified For the same reason the dense rim of concentrated medium cannot be seen The ducts are more clearly demonstrated but otherwise the appearances are as previously described

### Abnormal findings

*Calculi* —Telepaque given the previous evening causes no confusion nor difficulty in interpretation Non opaque calculi single or multiple show as filling defects in the ducts (Fig 125) Before a duct calculus can be diagnosed with certainty it must be completely surrounded by the medium or the lower end of the column of medium must show a definite upwards convexity (Fig 126) A sharp cut off appearance at the lower end of the common bile duct is not abnormal

*Obstruction* —The ducts are dilated when the calibre exceeds 8 millimetres Dilatation is usually present when there are calculi in the ducts and may also be due to inflammatory or traumatic strictures or to a tumour The dilatation frequently persists even when the cause has been removed An obstruction is indicated by opacification persisting 4 hours after injection delayed appearance of the medium in the duodenum and marked dilatation of the ducts A blunt cigar shaped

methylglucaminate of N N —adipic di—(3 amino 2 4 6 tri iodobenzoic acid) when injected intravenously is excreted in the bile in such amounts that concentration by the gall bladder is not necessary for radiographic demonstration of the ducts or gall bladder It is most advantageous to carry out intravenous cholecystangiography on the same morning and immediately after oral cholecystography This has the great advantage of saving time and in addition a slightly denser



Fig 124—Normal gall bladder and ducts Note translucent layer 2 centimetres thick in the gall bladder Erect film half an hour after Biligrafin

opacification of the ducts is obtained The recommended dose is 20 millilitres of Biligrafin forte intravenously which is a 50 per cent solution and contains 5 grammes of iodine but 40 millilitres can usually be given with safety A small amount should be injected very slowly and if there are no side effects after 2 minutes the injection is completed in 5 or 6 minutes Toxic reactions are uncommon and take the form of flushing urticaria nausea and occasionally vomiting More serious reactions are extremely rare but if they occur the injection should be stopped immediately Films are taken ½ and 2 hours after injection and others as required They may be taken with the serial device following screening or in the prone

position with an over-couch tube in the usual manner The films should be checked by the radiologist before the patient is dismissed A fatty meal is rarely necessary

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appearance of the lower end of the common bile duct suggests that the obstruction is due to a benign stricture (Fig 127)

The part played by spasm of the sphincter of Oddi in causing dilatation of the common bile duct is problematical according to Samuel (1955) In his series of cases attempts to relax the sphincter of Oddi by inhalation of octyl and amyl nitrite were not uniformly successful

*Carcinoma of the pancreas* —It may be possible to diagnose an early carcinoma of the pancreas the characteristic findings are high obstruction in the common bile duct with proximal dilatation and early filling of the gall bladder On the other hand a normal intravenous cholangiogram excludes a carcinoma of the head of the pancreas



FIG 125 —Gross dilatation of the ducts Gall bladder also slightly dilated Numerous non opaque calculi in the common bile duct Film 2 hours after Biligrafin

*Carcinoma of the gall bladder* —Intravenous cholecystography is the best and usually the only method by which a carcinoma of the gall bladder can be diagnosed radiologically since the gall bladder rarely concentrates on oral cholecystography due to the co existing cholecystitis The growth presents as an irregular persistent filling defect

*Peri cholecystitis* —In peri cholecystitis the gall bladder is grossly deformed and usually contains stones The cystic and hepatic ducts are usually kinked or narrowed and if the cystic duct is completely obstructed the gall bladder does not opacify

*Early jaundice*—At the beginning of an attack of jaundice from any cause the excretion is usually sufficient to show the ducts adequately When jaundice is well established the examination is useless In the author s experience excretion satisfactory for diagnostic purposes returns 2–3 weeks after the jaundice has



(*a*) (*b*)

FIG 126—Non-opaque calculus in the common bile-duct (*a*) Showing upward convexity (*b*) Surrounded by medium Films half an hour after Biligrafin and 14 hours after Telepaque

subsided As one would expect the excretion of Biligrafin remains good in un complicated cases of haemolytic jaundice

*Pancreatitis*—This method gives only little help in the diagnosis of chronic pancreatitis Confirmation that areas of calcification are in the head of the pancreas may be obtained Narrowing of the terminal inch or so of the common bile-duct is suggestive provided that the narrowing is persistent In such a case a previous examination showing the lower end of the common bile-duct to have been wider would be of significance It must be remembered however that in some normal cases the common bile-duct is only 2–3 millimetres in diameter but the lumen is regular and the hepatic ducts also are narrower than usual

**Correlation of intravenous and oral cholecystography**

*Oral cholecystography suggesting a normal gall bladder.*—The gall bladder presents a normal appearance on intravenous cholecystography and the ducts are usually, though not necessarily, also normal.

*Oral cholecystography suggesting disease of the gall bladder.*—Poor or absent excretion of Biligrafin indicates impaired liver function. Thus poor or non-



FIG. 127.—Gross dilatation of the common bile and hepatic ducts. Stricture at the lower end of the common bile-duct (confirmed at operation). Note typical cigar shaped appearance at the lower end of the common bile duct and absence of medium in the duodenum. Cholecystectomy 2 years previously. Film 4 hours after Biligrafin.

opacification of the gall bladder on oral cholecystography in such cases is due to inadequate excretion of Telepaque by the liver and the gall bladder may be normal.

Good excretion of Biligrafin may be associated with either a normal or a diseased gall bladder. In the former, the apparent failure of concentration of the Telepaque is due to inadequate absorption. The history (vomiting, diarrhoea and so on) is usually suggestive but, in addition, the gall bladder and ducts appear normal. In the latter—in practice the great majority of cases—disease of the gall bladder is virtually established by a process of exclusion but there are usually positive signs. The gall bladder gradually fills with opaque medium which does not become concentrated, and neither the layer effect nor the peripheral dense rim is seen. Furthermore, calculi are frequently shown in the gall bladder or ducts (Fig. 128). Non-opacification of the gall bladder signifies an obstruction in the cystic duct

or at the neck of the gall bladder usually by a calculus but sometimes by adhesions (Fig 129)

*Following cholecystectomy* —Intravenous cholangiography is of the utmost value and has contributed more than anything else to the elucidation of the so called *post cholecystectomy syndrome* Before the introduction of intravenous Biligrafin Pribram (1950) reviewed 1 370 cholecystectomies and estimated that the syndrome occurred in 20 per cent of cases

It is now clear that residual stones in the ducts strictures with dilatation and stasis and cystic duct stumps account for a large proportion of the poor results



FIG 128 – Enlarged gall bladder containing numerous non opaque calculi Film 2 hours after Biligrafin There was no concentration on oral cholecystography



FIG 129 —Non filling of gall bladder found at operation to be due to a calculus obstructing the cystic duct Note aberrant right hepatic duct (arrowed) Film 2 hours after Biligrafin

It has been frequently stated that dilatation of the ducts occurs after cholecystectomy but in common with other observers the author has not found this to be the case It would appear that any dilatation has either been there before operation or has occurred as the result of further calculus or stricture formation The gall bladder does not re form after cholecystectomy

*To summarize the intravenous method is of the utmost value in investigating* the significance of poor concentration or non concentration of Telepaque by the gall bladder in diagnosing calculi or abnormalities of the ducts and in the investigation of the post cholecystectomy syndrome As suggested by Sutton and Tillett (1954) it may ultimately supersede oral cholecystography as fallacies due to inadequate absorption do not occur Provided concentration is reasonably good however calculi in the gall bladder are better shown by oral cholecystography

in fact small stones may not be shown by the intravenous method Thus with the media available at present it is still advisable to use both methods in the investigation of disease of the biliary tract

## BARIUM MEAL

A barium meal is usually given to exclude lesions in the upper alimentary tract and is of no value in the diagnosis of most lesions in the biliary tract

**Cholecyst enterostomy or fistula**

Certain specific abnormalities such as an obvious cholecyst enterostomy or fistula may be clearly seen These are shown by barium entering the gall bladder and ducts fluoroscopy being essential to observe the mode of filling In such cases gas is usually present in the biliary tract Barium occasionally passes from



FIG 130 —Diverticulum arising from the second part of the duodenum causing obstructive jaundice At operation a firm hard chronic inflammatory mass around the diverticulum was involving the lower end of the common bile duct

the duodenum up the common bile duct as a result of temporary incompetence of the ampulla of Vater following the recent passage of a stone It may also be due to distortion by an ulcer of the second part of the duodenum or an ampullary carcinoma The latter presents as an irregular filling defect with destruction or distortion of the rugae in the medial wall of the second part of the duodenum

**Duodenal ulcer**

Very rarely a posterior wall duodenal ulcer involves the common bile duct causing jaundice The author has seen only one such case Rarely the duodenal bulb is indented by an enlarged gall bladder Diverticula commonly arise from the concave border of the second part of the duodenum but only rarely obstruct or distort the common bile duct (Fig 130)

**Carcinoma of the head of the pancreas**

In cases of carcinoma of the head of the pancreas no abnormality may be noted Enlargement of the duodenal loop or the reversed 3 appearance of the second part of the duodenum (Frostberg s sign) are almost diagnostic but are not commonly seen One or more persistent indentations of the concave aspect of the duodenal loop are the commonest signs Occasionally there is slight upward displacement of the pyloric antrum

**Peri cholecystitis**

In peri-cholecystitis there is usually distortion deformity and sometimes stenosis of the first and neighbouring second parts of the duodenum

## BARIUM ENEMA

A *barium enema* is of little value except to exclude lesions of the colon The hepatic flexure may be indented by an enlarged gall bladder or distorted by adhesions when peri cholecystitis is present A barium enema may be the only means of showing a cholecyst-colic fistula (Fig 122)

## DIRECT CHOLANGIOGRAPHY

**Percutaneous trans-hepatic cholangiography**

Various attempts have been made in the past (Lee 1942 Royer and Solari 1947) to demonstrate the biliary tract by injecting a radio opaque medium into a hepatic duct Nurick et al (1953) reviewed the literature and described a short series of cases A needle is inserted in the liver anteriorly and when a hepatic duct is entered as indicated by aspiration of bile 20 millilitres of a 35 per cent solution of diodone are injected It is preferable to carry out the examination under fluoroscopic control films of the ducts being taken as required It is by no means an easy matter to find a hepatic duct and extensive probing may be necessary The only indication for this procedure is obstructive jaundice where other methods have failed to determine the site and nature of the obstruction If successfully performed percutaneous trans hepatic cholangiography can be of great diagnostic value but the danger of haemorrhage and biliary peritonitis far outweighs its advantages

**Operative cholangiography**

Twenty millilitres of a 35 per cent solution of diodone are introduced into the common bile duct after it has been exposed at operation Operative cholangio graphy an easy procedure is performed to show the size of the ducts the presence or absence of calculi or other obstructive lesion and the patency or otherwise of the ampulla of Vater (Fig 131) Its disadvantages are the time added to the opera tion and the fact that the films are frequently of inferior quality since they are usually taken with a mobile unit and are sometimes blurred by movement Further more one fatal case of pancreatic necrosis following operative cholangiography has been recorded (Hershey and Hillman 1955) Care must be taken not to intro- duce air bubbles which might be mistaken for non opaque calculi

in fact small stones may not be shown by the intravenous method Thus with the media available at present it is still advisable to use both methods in the investigation of disease of the biliary tract

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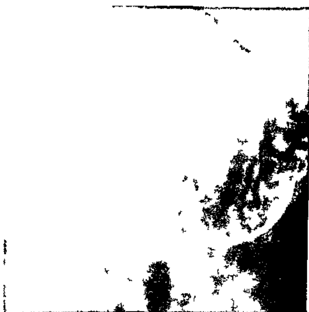


FIG 130 —Diverticulum arising from the second part of the duodenum causing obstructive jaundice At operation a firm hard chronic inflammatory mass around the diverticulum was involving the lower end of the common bile duct

the duodenum up the common bile duct as a result of temporary incompetence of the ampulla of Vater following the recent passage of a stone It may also be due to distortion by an ulcer of the second part of the duodenum or an ampullary carcinoma The latter presents as an irregular filling defect with destruction or distortion of the rugae in the medial wall of the second part of the duodenum

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Failure of both the gall bladder and the ducts to opacify indicates impaired liver function and no opinion can be given on the biliary tract During the barium meal special attention must be paid to any displacement or indentation of the pyloric antrum or duodenum which would suggest a carcinoma of the pancreas Serial films with compression centred on the second part of the duodenum are essential as they may show an ampullary carcinoma

**Moderate or marked jaundice**

Oral and intravenous cholecystography are useless as the media are inadequately excreted by the liver Plain radiography and a barium meal are the only useful radiological methods Thus an accurate diagnosis frequently cannot be made

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*Post operative cholangiography*

Fifteen to twenty millilitres of a 35 per cent solution of diodone are injected through the T tube draining *the common bile duct usually on the seventh to the* tenth post operative day Post operative cholangiography is performed to exclude



Fig 131 —Carcinoma of the common bile duct causing complete obstruction Operative cholangiogram



Fig 132 —Non opaque calculus at the lower end of the common bile duct Post operative cholangiogram

residual stones and to confirm that *the ampulla of Vater is patent (Fig 132) Again* care must be taken not to introduce air bubbles Filling of the pancreatic duct occasionally occurs

## INVESTIGATION OF CASES WITH JAUNDICE

Such cases form a minor but nevertheless a most important group

*Early or mild jaundice*

The standard procedures—plain radiography oral and intravenous cholecysto graphy and cholangiography followed if necessary by a barium meal are employed The plain films must be scrutinized most carefully for calculi Excretion of Tele paque and Biligrafin by the liver is usually adequate for diagnostic purposes

that its use is limited to non jaundiced patients The retention of this dye is high in many types of liver disease and for the estimation of liver damage in non icteric patients it is undoubtedly the most sensitive This applies particularly to hepatic cirrhosis However in some cases of well compensated cirrhosis the re tention of dye may be normal In congestive heart failure the degree of retention of BSP does not always parallel the histological appearance of the liver obtained by needle biopsy (King and King 1956) This latter finding has been confirmed by the experimental work of Andrews et al (1956) who observed in the dog that when the liver was congested with engorged sinusoids a rising portal pressure and reduced rate of portal flow the BSP extraction was normal provided hepatic arterial flow was normal They also suggested that the cells of the small bile ducts in the portal canal play an active part in the removal of BSP from the plasma These thin walled ducts are very richly supplied by the hepatic artery and are intimately associated with branches of the hepatic artery before the sinusoids are reached this seemed to suggest a possible explanation for some of the experimental results previously reported in which perfusion of liver slices was used Brauer and Pessotti (1949) reported that liver slices in an atmosphere free from oxygen take up BSP as rapidly as do controls and that poisons fail to reduce dye uptake

Andrews (1955) also suggested that the biliary tract secretes most if not all of the constituents of the bile and bases some of his arguments on the blood supply of the small bile ducts and the greater importance of the arterial circulation rather than the portal venous circulation in BSP removal Attempts have been made to add a correction factor for the use of BSP excretion in patients with jaundice (Zieve et al 1951) Hoffbauer et al (1955) found this test to be less sensitive than the flocculation tests in the differential diagnosis of jaundice which is what one would expect in a test which depends on excretion of the dye Using $^{35}S$ labelled BSP in dogs Brauer et al (1955) showed that 80 per cent of infused dye is present in the bile from a biliary fistula and that 20 per cent of this dye has been altered by the liver There is also some storage of $^{35}S$ labelled BSP in skeletal muscle Carbon tetrachloride poisoning of the liver did not diminish the uptake of the dye nor its concentration but did diminish its excretion rate

One other interesting finding was that laparotomy and preparation of the biliary fistula did not affect the BSP clearance by the liver despite claims to the contrary In a careful study of the relative value of liver function tests Zieve and Hill (1955) showed statistically that BSP clearance by the liver provides the most effective single test in the absence of jaundice Cohen et al (1956) studied the effect of simultaneous administration of BSP and rose bengal They showed that BSP had a greater affinity than rose bengal for the transfer mechanism involved in their removal from the blood stream and excretion in the bile The suggested transfer mechanism was first uptake by the liver of the dye from its combination with serum albumin secondly there was excretion of the dye into the biliary system

To summarize it may be said that the BSP clearance gives the best test of liver function in the absence of jaundice The position of BSP as an experimental factor in estimating the blood flow of the liver and the excretory mechanisms of the liver remains unchallenged

# CHAPTER 22

# LIVER FUNCTION

W E KING

DURING the past five years much investigation has been undertaken on the function of the liver which has clarified many ideas and provided a sounder basis for the clinical interpretation of liver function It has not greatly altered the scope of liver function tests which are still partly empirical More efficient tests are being constantly sought and it is only by an appreciation of the metabolic and bio chemical activities of the liver that these will be found It is not proposed to discuss the routine laboratory tests referred to as liver function tests but rather to indicate where progress is leading in our understanding of the liver and its function

## PIGMENT METABOLISM

The estimation of the level of pigments in the circulating blood should provide a reliable guide to what is happening in the liver For many years after the description by Van den Bergh of the test that bears his name it was thought that the differentia tion of the various types of jaundice was possible by this method Gradually less significance was attached to the qualitative aspects and the test was used entirely as an index of the level of serum bilirubin Watson (1946) suggested a bilirubin protein bond which was broken by the liver as the reason for the two types of bilirubin described Cole and Lathe (1953) showed that the directness or indirect ness of the Van den Bergh reaction is not related to a linkage between bilirubin and protein By reverse phase chromatography two types of pigment were pre pared and neither contained protein Billing (1954) showed that there were two components of the direct reacting pigment which also moved more quickly owing to its solubility These pigments have been called pigment I and pigment II Further investigation by these three workers has confirmed that the indirect reacting and slow moving pigment is identical with bilirubin Finally Billing and Lathe (1956) have shown that the probable pathway for bilirubin excretion by the liver in man is through conjugation with glucuronic acid

There are indications that this separation of the bile pigments may have some clinical application in differentiating obstructive jaundice from hepatocellular jaundice One should expect an increase in pigment II in obstructive jaundice and an increase in pigment I in infective hepatitis but this requires much closer study before definite views can be expressed One further interesting sidelight on this problem is the suggestion by Bollman (1956) that in cholangiolitic hepatitis pig ment I predominates but in jaundice caused by chlorpromazine it is pigment II that shows the greater increase

## BROMSULPHALEIN CLEARANCE

*Bromsulphalein* (BSP) appears to approach most closely to the correct answer of liver function It has to be remembered that only one function is being tested and

that its use is limited to non jaundiced patients The retention of this dye is high in many types of liver disease and for the estimation of liver damage in non icteric patients it is undoubtedly the most sensitive This applies particularly to hepatic cirrhosis However in some cases of well compensated cirrhosis the retention of dye may be normal In congestive heart failure the degree of retention of BSP does not always parallel the histological appearance of the liver obtained by needle biopsy (King and King 1956) This latter finding has been confirmed by the experimental work of Andrews et al (1956) who observed in the dog that when the liver was congested with engorged sinusoids a rising portal pressure and reduced rate of portal flow the BSP extraction was normal provided hepatic arterial flow was normal They also suggested that the cells of the small bile-ducts in the portal canal play an active part in the removal of BSP from the plasma These thin walled ducts are very richly supplied by the hepatic artery and are intimately associated with branches of the hepatic artery before the sinusoids are reached this seemed to suggest a possible explanation for some of the experimental results previously reported in which perfusion of liver slices was used Brauer and Pessotti (1949) reported that liver slices in an atmosphere free from oxygen take up BSP as rapidly as do controls and that poisons fail to reduce dye uptake

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## PROTEIN METABOLISM

### Serum protein patterns

Some of the most important functions of the liver are concerned with protein metabolism The use of chemical estimations of the serum protein concentration and the division into albumin and globulin fractions have been standard procedures in investigating liver disease for many years The finding of a lowered level of serum albumin and an elevated serum globulin level has been regarded as typical of extensive liver disease but the increased interest in serum protein levels has cast doubt on the specificity of this finding and has shown that the chemical separation of the serum proteins into albumin and globulin fractions is too crude a method The first improvement came with chemical separation of the globulin fractions and the use of the level of serum *gamma* globulin in diagnosis and prognosis of liver disease *This proved to be of real value particularly in patients with* long standing jaundice where the exact diagnosis was in doubt It was also found to be helpful in assessing the continuance of activity in infective hepatitis—quite often it is the last function test to return to normal Elevation of the serum *gamma* globulin is found consistently in patients with chronic active hepatitis (Saint et al 1953)

### Filter paper electrophoresis

Newer methods of estimation now depend on filter paper electrophoresis

In this an electric current is passed across a buffer soaked strip of filter paper to which serum has been applied and by staining this strip with various dyes it is possible to measure the amount of dye bound to the various components and so construct an *electrophoretic pattern which agrees very closely with the Tiselius pattern* Various modifications of this type of apparatus are now in common use (Durrum 1951 Kunkel and Tiselius 1951) By this means it has been possible to follow serum protein patterns in liver disease and to distinguish other causes of increased serum globulin (multiple myeloma systemic lupus erythematosus and many others) Although the precision of analysis does not equal that of the free electrophoresis of Tiselius the method is simple and requires only a small amount (0 2 millilitre) of serum and is sufficiently accurate for clinical needs

In acute hepatitis the albumin fraction usually remains normal but there is often an increase in *beta* globulins and *gamma* globulins The latter band becomes much more intense if the acute attack be slow to resolve or becomes chronic In cirrhosis there is a lowering of the albumin level and a marked rise in serum globulin sometimes in more severe cases a $gamma_1$ band can be distinguished In primary biliary cirrhosis there is often a high *beta* globulin peak which has been found to be due to lipoproteins formed in association with the high phospholipid and free cholesterol content of the sera in these patients (Ahrens et al 1950)

### Labelling with radio active isotopes

For many years it has been accepted on clinical grounds that lowering of the level of serum albumin occurred in severe or extensive liver damage Madden and Whipple (1940) produced evidence in support of this from experimental work Miller and Bale (1954) showed that when rat s liver was perfused with amino acids

including $^{14}C$ labelled lysine the labelled amino acid was incorporated into albumin *alpha* globulins and *beta* globulins and fibrinogen These workers found a higher radio activity in the *alpha* globulin fraction which is in accord with the view that the normal animal produces *alpha* globulin more rapidly than albumin or *beta* globulin and that the turnover rate of *alpha* globulin is more rapid than that of other protein fractions Except for the *gamma* globulins the curve of total $^{14}C$ incorporation in plasma proteins in the isolated perfused liver is grossly similar to the curve produced in the intact animal This work confirms the role of the liver in albumin production As the mucoproteins may be counted with the *alpha* globulin during electrophoresis at *p*H 8 5 the observation of lowered mucoproteins in liver disease may be understood in the light of this work

Using the non hepatic tissues of a perfused carcass it was shown by Miller and Bale (1954) that there is clearance of $^{14}C$ labelled lysine and glucose from the perfusate and synthesis of both plasma and tissue proteins The *gamma* globulins contain most of the $^{14}C$ activity with small but measurable activity in the *alpha* globulins and the *beta* globulins No activity was found in the albumin and fibrinogen fractions The other inference of their work was that in the rat at least *gamma* globulin formation is mainly in the bone marrow—the spleen and lymph nodes did not appear to be quantitatively important as a site of *gamma* globulin formation in these experiments Sterling (1951) had previously shown that the turnover of $^{131}I$ labelled albumin was slower in Laennec s cirrhosis than in normals and that there was a longer half life for this labelled albumin When the serum albumin level was 2 5 grammes per cent or less the deviations from normal were more pronounced

Inflammation in the body increases protein loss from the liver Using a sterile turpentine abscess as an example of acute inflammation Yuile et al (1953) showed the half life of albumin in the dog to be reduced to 2 days (normal 9 days) Fibrinogen is also turned over in a spectacular manner This increased turnover of albumin in inflammation may be related to the lowered serum albumin level found in inflammatory diseases particularly those of the liver

Protein depletion of the liver by starvation leads to diminished enzyme activity (Wainio et al 1953) This appears to be the reason for the susceptibility of the liver in protein depleted dogs to hepatotoxic agents It leads one to speculate as to the effect of the enormous protein loss that can occur in ulcerative colitis The characteristic serum protein pattern of chronic liver disease is a lowering of serum albumin and an elevation of *gamma* globulin It has been suggested that there may be some influence on the rate of turnover of the various proteins by their level in the plasma The association in chronic inflammatory conditions of hyper *gamma* globulinaemia and hypo albuminaemia has led to much speculation on this question In liver disease there is good evidence of increased degradation of $^{131}$ I labelled *gamma* globulin (Havens et al 1954) but Martin and Davies (1955) have shown that albumin transfusion had no effect on the hyper *gamma* globulinaemia of chronic hepatitis

**L E Cell phenomenon**

Very high levels of *gamma* globulin have been noted in chronic hepatitis and increase in plasma cells in the liver has been found in these patients (Kunkel and Tiselius 1951) In our own series of chronic hepatitis (Saint et al 1953) similar findings were recorded In one case in which the level of *gamma* globulin was 4 5 grammes per cent there was a definite increase in plasma cells in the bone marrow

It has also been suggested that the finding of lupus erythematosus cells in chronic hepatitis is related to this hyper *gamma* globulinaemia (Joske and King 1955) This study has been pursued at the Clinical Research Unit in the Royal Melbourne Hospital and the L E Cell phenomenon been demonstrated in five more proven cases of chronic hepatitis The opposing view is suggested by Bearn et al (1956)—that these cases of unexplained chronic liver disease in young women with arthralgia and raised *gamma* globulins may be a variant of systemic lupus erythe matosus

**Serum transaminases**

Transamination is the process by which an amino group of an amino acid is trans ferred to a keto acid The reversal of this reaction may be the final step in the synthesis of an amino acid This takes place to a great extent in the liver which is the second richest source in the body of serum glutamic oxalacetic transaminase (SGO T) and easily the richest source of serum glutamic pyruvic transaminase (SGP T) (Wroblewski 1956) These enzymes can now be measured in the serum chromatographically by spectophotometry and by colorimetric methods (Wroblewski 1956) There is a large increase in the serum concentrations of both enzymes with hepatic injury

In acute hepatitis there is an impressive increase in both enzymes in the serum though the rise in SGP T exceeds the rise in SGO T Of great value is the fact that this rise has been found to precede the appearance of jaundice and may therefore enable an earlier diagnosis of acute hepatitis to be made The normal range of SGO T is 5–35 units but in hepatitis this may be increased 10–100 times normal Peak levels appear to be obtained at the height of the illness and the fall in enzyme levels parallels the patient s clinical condition rather than the level of serum bilirubin Relapses are accompanied by a parallel rise in enzyme activity

In cirrhosis of the liver there is an increase in enzyme activity though here SGO T levels are higher than SGP T Continued elevation of transaminase activity is said to be a poor prognostic sign (Wroblewski 1956) There is a rise in enzyme activity in obstructive jaundice but not to the same high level as in acute hepatitis It is noteworthy that transaminase activity is also increased in metastases in the liver It has the advantage over serum alkaline phosphatase estimations of not being affected by secondary deposits in bone The only care that must be taken is to exclude acute injury to heart or skeletal muscle which will liberate SGO T into the circulation SGP T occurs in much lower concentrations in heart and skeletal muscle and is therefore not likely to cause this source of error Wroblewski recommends the simultaneous measurement of them both in the study of hepatic disease

**Ornithine cycle**

One final aspect of protein metabolism which has an effect on liver function is the ornithine cycle (Krebs Henseleit cycle) In this cycle arginine is hydrolysed to urea and ornithine The latter is converted to citrulline and eventually to arginine and in so doing consumes ammonia This has now been used in the treatment of liver failure by giving arginine intravenously It can be effective only if the level of blood urea is not raised Preliminary results have been most promising (Najarian and Harper 1956)

## LIPIDS AND LIPOPROTEINS

The description of accumulation of cholesterol in the blood in obstructive jaundice dates back to Austin Flint (1862) Chambard (1878) first realized the association of high serum lipid levels and xanthomas in biliary cirrhosis There has been a gradual and steady accumulation of knowledge of the role of these substances in liver function and liver disease The realization that the great proportion of cholesterol and phospholipid fractions are bound to lipoproteins and migrate with an electrophoretic mobility similar to these lipoproteins has led to considerable advance in this field Kunkel and Slater (1952) first described a method using zone electrophoresis in a filter paper or starch medium containing barbital buffer by which electrophoretic components could be isolated directly allowing lipid analyses to be carried out Prior to this it had been very difficult to determine the exact migration of lipoproteins when patterns of whole serum were obtained by the Tiselius method The normal lipoproteins can be divided by this method into two main types (1) *alpha* lipoprotein which migrates slightly ahead of *alpha* globulin and falls partially into the albumin fraction this lipoprotein has a cholesterol phospholipid ratio of 0 5 and has a consistently lower free total cholesterol ratio than does the *beta* lipoprotein (2) the second type is the *beta* lipoprotein with a mobility similar to *beta* globulin but slightly slower it has a cholesterol phospholipid ratio of 1 3

Investigation of the lipoproteins in liver disease reveals marked deviation from the normal pattern In obstructive jaundice and early acute hepatitis the lipid content of these lipoproteins varies widely from normal There is a change in the type of lipoprotein In Cohn s fraction IV + V + VI the lipoproteins have the electrophoretic characteristics of *beta* lipoprotein whereas normally they are high density *alpha* lipoproteins In Cohn s fraction I + III the lipoproteins have the physical characteristics of *beta* lipoprotein as is usual but they show less cholesterol ester and the cholesterol phospholipid ratio is as low as 0 5 (Eder et al 1955) The conclusion reached is that in biliary cirrhosis early acute hepatitis and some cases of obstructive jaundice there are at least two types of abnormal lipoprotein In recovery from acute hepatitis and after removal of the biliary obstruction these abnormal lipoproteins are replaced by the normal ones Such lipoproteins have not been found in portal cirrhosis with only moderate degrees of jaundice /The appearance of these abnormal lipoproteins of altered chemical composition offers an explanation for some of the alterations in plasma lipid relationships of liver disease As little of the cholesterol is esterified in these abnormal lipoproteins it follows that the plasma free to total cholesterol ratio will be elevated It may well be that the high ratio is an indication of the production of abnormal lipoproteins and not an indication of parenchymal liver damage as has been claimed previously

In primary biliary cirrhosis there is a very great increase in blood lipids This is mainly in the phospholipid and free cholesterol fractions with very little increase in cholesterol esters or neutral fat In this condition there is a high peak of *beta* lipoprotein and a great reduction or absence of *alpha* lipoproteins Kunkel (1956) using the preparative ultracentrifuge has shown that lipoproteins from these sera are of very high molecular size He obtained clear lipoprotein fractions where there was as little as 20 per cent protein free cholesterol and phospholipid

making up the remainder of the lipoprotein He pointed out that the lipids are bound to the protein in such a way as to be uniquely soluble in aqueous solution This appears to be the explanation of the remarkable clarity of the sera from patients with extremely high lipid content This solubility would also suggest why patients with biliary cirrhosis do not appear increasingly liable to atheroma despite an excessively high figure for blood lipids

Further investigation of lipoproteins in acute hepatitis reveals no change in the lipoprotein pattern between infectious hepatitis and serum hepatitis The increase in low density (*beta*) lipoproteins and decrease in high density (*alpha*) lipoproteins appears to parallel the level of serum bilirubin and they return to normal with recovery from the disease The increase in these lipoproteins correlates significantly with the thymol turbidity test but not with most of the other routine tests of liver function (Pierce et al 1954) The same changes in the lipids were noted here as in biliary cirrhosis but to a much less degree All this work points to a need for clarifying our ideas on lipid estimations in liver disease These investigations are beyond the scope of routine laboratory work and at present cannot be used in this manner The changes in blood lipids are of little value in the differential diagnosis of jaundice but may indicate a diagnosis of primary biliary cirrhosis and may be of value in assessing prognosis in chronic liver disease

Using $^{14}C$ labelled acetate Eckles et al (1955) have shown that removal of the liver in dogs almost completely prevents the appearance of $^{14}C$ labelled cholesterol in the plasma Cholesterol synthesis did occur in other organs The peak value for isotope concentration in liver free cholesterol occurred in 40 minutes Work by Gould et al (1955) using $^{14}C$ labelled acetate injected intravenously showed a slower formation of peak production in man compared with dogs In normal subjects the fraction of the dose of labelled acetate used for cholesterol synthesis was 1 04 per cent In myxoedema it was 0 23 per cent 4 75 per cent for patients treated with cortisone

With the growing interest in lipid metabolism a better understanding of their place in liver function is being achieved There is still a long gap to be bridged since Bogoch et al (1955) have shown that there is no correlation between levels of serum lipids and quantities of liver lipids demonstrated histochemically

## THE LIVER AND STEROID COMPOUNDS

Bongiovanni and Eisenmenger (1951) have drawn attention to a type of cirrhosis peculiar to young women There is no antecedent hepatitis and the patients may exhibit evidence of overactivity of the adrenal cortex The level of urinary adrenal corticoids is high Most series of cases of chronic hepatitis contain examples of this syndrome It now appears that there is failure of the liver to inactivate adrenal steroids Using surviving actively respiring slices of liver from the rat Chart et al (1956) have shown complete inactivation of the biological potency of aldo sterone Anaerobic conditions impair this inactivating capacity of liver slices Liver from man was obtained at laparotomy and showed an exactly similar capacity to inactivate the salt retaining hormone A similar metabolic effect of the liver on oestrogens has been shown by numerous workers (Ryan and Engel 1953) Similar enzymatic transformations of testosterone have been described (Wotiz et al 1954)

Conn et al (1954) have demonstrated that the liver converts cortisone hydrocortisone and corticosterone to 17 ketosteroids and that this conversion is diminished with liver disease The rate of disappearance of hydrocortisone from the plasma was inversely proportional to the degree of liver damage as measured by BSP retention (Brown et al 1954) The effect of liver disease or anoxia on this inactivation makes it very tempting to speculate on the endocrine upsets and fluid retention that may occur in chronic liver disease

In cardiac disease where the liver is secondarily affected by the hypoxia it may well be that this is partly responsible for causing the alterations in concentration of the salt retaining hormone which have already been demonstrated

These investigations give a better insight into the variations of endocrine function noted for many years in liver disease and also help in the understanding of fluid retention in the body in disease states It may offer a possible explanation of the varying results in the orally administered hormones in the fulminant forms of ulcerative colitis

## RADIO ACTIVE ISOTOPES IN LIVER FUNCTION

Mention has already been made of the use of $^{131}$I in labelling serum albumin and globulin This has greatly advanced our knowledge of the metabolism of these proteins The use of $^{14}$C in labelling albumin and other proteins was also discussed in relation to the liver and protein metabolism in acute inflammation Volwiler et al (1955) used radio active sulphur to investigate the turnover rates of various plasma proteins in both normal controls and patients with cirrhosis These studies have helped greatly in our understanding of liver function but are of course not applicable to ordinary clinical medicine More recently $^{131}$I labelled rose bengal has been used This has been as an uptake and excretion test using external scintillation counting techniques Taplin et al (1955) have reported their experiences on rabbits and subsequently in man There are definite curves for various forms of liver disease but in most cases it appears to parallel the results obtained with the usual liver function tests There is a possibility of this test yielding useful results in chronic liver disease or toxic hepatitis The disadvantages of this technique are that special apparatus and trained personnel are necessary and also it is doubtful whether rose bengal is as reliable a dye for excretion studies as BSP However Reimer et al (1956) have reported further encouraging results using the same technique

The use of radio active iron to assess the benefit of repeated phlebotomies in the treatment of haemochromatosis should help to increase our knowledge of iron metabolism in this condition (Bothwell et al 1955) The use of repeated phlebotomies would appear to be justifiable though whether it is really possible to reverse the fibrotic changes in the liver is open to doubt

Bearn and Kunkel (1955) have used radio active copper in the study of Wilson s disease They have found that the radio activity associated with the serum albumin after an oral or intravenous dose of $^{64}$Cu is increased and persists much longer in patients with this disease than in normal control subjects The lack of ceruloplasmin in patients with Wilson s disease was also observed in this study

A further use of isotopes has been the study of ascites in liver disease Prentice et al (1952) used tritium labelled water to show that the water content of ascites

enters and leaves the peritoneal cavity at a very rapid rate (approximately 40-80 per cent per hour) Ascitic fluid is thus a rapidly circulating medium and not a stagnant reservoir There is also a free exchange of proteins between plasma and ascitic fluid—here use has been made of $^{131}$I labelling of serum albumin and *gamma* globulin (Bauer et al 1954)

In summary it may be said that isotopes have been most valuable in our understanding of the metabolic processes of the liver in health and disease As a method of clinical testing of liver function their use can be considered only in properly equipped hospitals with the proper apparatus and trained technical staff It may be with advances in knowledge that isotope techniques will play as important a role in the diagnosis of liver disease as they do in disorders of the thyroid gland

## CONCLUSIONS

In this brief review of some of the aspects of liver function it can be seen that constant progress in our understanding of the role of the liver is being made A vast amount of work has been carried out over the past 5 years most of which still cannot be readily applied to the clinical evaluation of liver function In the patient with jaundice we must still depend on standard tests of liver function in reaching a diagnosis The chemical estimation of *gamma* globulin has been a very useful addition to this battery of tests but still more can be learned from the filter paper type of electrophoresis of proteins The level of serum transaminases may give further help and may enable an earlier diagnosis of acute hepatitis to be made Even with an added correction factor for the degree of jaundice BSP clearance is of no value in the patient with jaundice For this reason and for others previously mentioned radio active isotopes cannot help either Latest work on the lipoproteins and their relation to free or total cholesterol levels shows that our ideas on this fraction of the serum will have to be changed The lowering of cholesterol esters may well be associated with the type of abnormal lipoprotein

For the patient with jaundice it is recommended that the following tests should be carried out

(1) Serum bilirubin

(2) Flocculation tests (cephalin cholesterol thymol turbidity or zinc sulphate)

(3) Serum alkaline phosphatase

(4) Serum proteins with estimation of albumin and globulin fractions particularly the level of *gamma* globulin preferably by electrophoresis

Estimation of serum cholesterol and lipids may help in biliary cirrhosis either primary or secondary and the abnormal lipoproteins may be detected on filter paper electrophoresis

In the non icteric patient BSP clearance has pride of place as the best test of liver function at the present time It may be that the use of radio active isotope labelling of dyes excreted by the liver will replace its use in the future with improvement in knowledge and technique

It seems that even today some of our tests of liver function are still empirical but the gap between liver function in its correct sense and liver function as a group of biochemical tests is gradually being narrowed

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# CHAPTER 23

# LIVER FAILURE

SHEILA SHERLOCK

IN THE present state of knowledge liver failure must be considered as a clinical syndrome It is difficult to equate specific functions of the liver cell with clinical findings For instance ascites one of the most important associations of liver failure cannot be related only to hepato cellular function and liver coma is not due only to disease of the liver cells Moreover pure hepato cellular failure is extremely rare and there are usually additional features due to disordered intra hepatic circulation to intrahepatic or extrahepatic bile duct obstruction or to the associated reticulo endothelial reaction

The syndrome has a variety of causes the most common being hepatic cirrhosis whether portal or post necrotic It may also complicate acute virus hepatitis Interference with the hepatic blood supply by ligation of the hepatic artery in the portal fissure or occlusion of the hepatic vein may lead to liver cell failure but the syndrome does not complicate portal venous occlusion It sometimes occurs with hepato lenticular degeneration (Wilson s disease) with bilharzial liver or with haemochromatosis but is almost unknown as an accompaniment to cardiac cirrhosis

Liver cell failure may occur terminally in obstructive jaundice such as chronic intrahepatic obstructive jaundice (primary biliary cirrhosis) or extrahepatic ob struction associated with malignant replacement of liver tissue or acute cholangitis It should be diagnosed rarely and with caution in a patient suffering from acute *biliary obstruction and certainly not until other possible complications of the* obstructive jaundice have been carefully excluded

## GENERAL DETERIORATION OF HEALTH

The patient with liver failure has a poor appetite vague indigestion and flatulence and loses weight Weakness is conspicuous and there is obvious muscle wasting These features have a complex aetiology This may be related to the failing meta bolic functions of the liver there is difficulty in mobilizing and storing carbohydrate and in manufacturing tissue protein Anorexia and poor dietary habits add to the malnutrition

## JAUNDICE

The significance of this sign may be exceedingly difficult to interpret It may indicate failure of the liver cells to excrete bilirubin intrahepatic or extrahepatic bile duct obstruction or increased destruction of erythrocytes In any one patient the jaundice may be due to a combination of these factors

In acute liver failure due to disease such as virus hepatitis jaundice usually parallels the extent of liver damage (Sherlock 1946) Occasionally however the intrahepatic biliary obstruction component of acute hepatitis may be so prominent that this is not so in such patients there is pruritus and a high serum alkaline

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responses become extensor The diffuse nature of the cerebral disturbance is further shown by reversed sleep rhythm excessive appetite muscle twitchings grasping and sucking reflexes and disorders of speech and vision

**Electroencephalographic changes**

Electroencephalography is helpful in diagnosis Foley et al (1950) described bilaterally synchronous slow waves of 2 per second frequency in the delta range In the early stages these occur in bursts usually separated by the normal cortical rhythm The bursts at first appear in the frontal region but later increase in duration and spread laterally and posteriorly until the entire record is one of slow activity More recently Bickford and Butt (1955) have recognized the following stages in the electroencephalogram (1) stage with diffuse waves of a frequency 4–7 per second—the patient with this electroencephalographic recording is usually *moderately confused* (2) *triphasic stage with diffuse bilaterally synchronous* triphasic waves whose maximal deflection is surface positive (3) stage with random arrhythmic waves with little bilateral synchrony dominating the record

Patients in the triphasic and delta stages are usually semi comatose or completely unresponsive If the patient recovers the electroencephalogram returns to normal These electroencephalographic changes are occasionally found with other metabolic abnormalities of the brain and are not entirely specific for hepatic coma

**Pathogenesis**

The essentially reversible nature of the cerebral disturbance and the diffuse involvement suggest that the changes are metabolic Similar nervous disorders have been induced in some patients with liver disease by oral administration of a high protein diet ammonium chloride urea methionine or choline (Van Caulaert et al 1932 Kirk 1936 Phillips et al 1952 Phear et al 1956) This suggests that the material responsible is nitrogenous Ammonium has been incriminated as the possible toxic substance Theoretically it would be possible for ammonium to interfere with cerebral metabolism

Bessman and Bessman (1955) showed that in hepatic coma there is an increased arterial jugular bulb ammonium difference indicating that ammonium is being utilized by the brain in some chemical reaction Of the many reactions utilizing ammonia in the body two are of significance in the brain—glutamine synthesis and the reversal of glutamate oxidation namely reductive amination of α keto glutarate Synthesis of glutamate from α ketoglutarate could produce the phenomena seen in hepatic coma by interfering with the Krebs cycle which is the most likely final oxidative pathway in the brain This is the rationale for glutamic acid therapy (Walshe 1953) The diminished cerebral oxygen metabolism in hepatic coma (Wechsler et al 1954) would agree with this hypothesis This however cannot be the entire explanation for Webster and Davidson (1956) report that the brain in hepatic coma does not always take up ammonia but occasionally the jugular bulb value may exceed that in the artery The blood ammonium level is frequently although not constantly raised in patients in hepatic coma (Phear et al 1955) (Fig 133) Identical neurological changes can be precipitated by administering oral methionine without producing a constant rise in the blood ammonium level (Phear et al 1956) The relation of blood ammonium levels to liver coma might thus be similar to the relation of blood urea levels to clinical

phosphatase level These features are helpful in assessing the significance of the jaundice

In the chronic failure of Laennec s cirrhosis jaundice is usually mild Clinical icterus is of grave prognostic significance The survival time of erythrocytes is diminished and haemolysis contributes to the jaundice (Chaplin and Mollison 1953 Jandl 1955)

The jaundice associated with liver failure can often be reduced by ACTH or cortisone (Sborov et al 1955) but such therapy does not affect the underlying disease process and cannot be recommended as a routine measure

## NEURO PSYCHIATRIC CHANGES

The view that a neurological syndrome may complicate liver disease of varied aetiology has now been accepted and the term hepatic coma has come to encom pass the whole clinical syndrome of which coma is only a small part (Adams and Foley 1953 Sherlock et al 1954) The better recognition of the earliest changes which precede coma has improved the prognosis as much as the better understand ing of the mechanisms and consequently more rational therapy

### *Clinical picture*

Clouding of consciousness usually shown by extreme apathy and confusion occurs in all patients and sometimes progresses to coma The lapse into coma may be abrupt but more often the insidious evolution of mental confusion and apathy or sometimes extreme emotional lability is the first sign of deterioration Though varied by grimacing and blinking facial expression becomes vacant salivation increases and speech is slow slurred and increasingly restricted to the repetition of a few irrational phrases Simul taneously comprehension becomes clouded so that simple requests are obeyed with difficulty if at all and socially bizarre behaviour exemplified by lack of restraint nocturnal ramblings and a peculiar tendency to evacuate bladder and bowels in in appropriate places create embarrassing situations

The episodes commonly begin in the late evening are of variable duration and may terminate at any stage the patients having no recollection of their actions Recovery is often rapid consciousness returning before other neurological signs abate Variation from day to day and even from hour to hour is particularly noticeable

The most characteristic neurological sign is the flapping tremor reminiscent of the beating of a bird s wings This is best demonstrated with the patient s arms outstretched and the fingers separated as a series of rapid flexion extension movements at the meta carpophalangeal and wrist joints often accompanied by lateral movements of the digits There is in addition a fine 6-9 per second tremor of the outstretched fingers Spread of this tremor to the elbows and shoulders is best seen if the patient puts his hands on his head On sitting forward in bed the whole body may shake the legs may jerk and inco ordination is gross in the finger nose and heel knee test The patient is ataxic There may be a trombone tremor of the protruded tongue and twitching of the face when the corners of the mouth are retracted All these motor abnormalities disappear in repose or in remission They are liable to be missed if the patient is only observed at rest and not asked to hold his hands in front of him The flapping tremor also occurs sometimes in patients with uraemia or respiratory failure

Less specific findings include increased tendon reflexes and muscle tone with ankle clonus and normal plantar responses As coma deepens muscle tone becomes flaccid previously brisk clonus and tendon reflexes can no longer be elicited and the plantar

uraemia (Singh et al 1954) in both cases a correlation can be established but in neither is the relationship causal

Although there is speculation concerning the nature of the toxic substance or substances the intestinal production and route by which it reaches the brain seems certain Observations using oral ammonium chloride as the test nitrogenous substance and the hepatic vein catheterization technique have shown two routes by which toxic substances of intestinal origin might reach the systemic circulation in patients with liver disease In patients with severe hepato cellular disease (for example severe virus hepatitis) the failing liver allows the substances to pass unaltered into the peripheral blood In patients with cirrhosis in addition to impaired liver function the presence of a collateral circulation delivers portal vein blood directly to the peripheral blood stream before it can be metabolized by the liver The neurological syndrome can therefore be termed a *portal systemic encephalopathy* (Sherlock et al 1954 White et al 1955) The development of the syndrome in a patient with cirrhosis depends upon the balance between the extent of the collateral circulation and the capacity of the liver to metabolize toxic factors There are thus 3 factors to be considered in any patient with liver disease showing neuro psychiatric changes (Fig 134) (1) nitrogenous substances in the intestine (2) portal systemic collateral veins diverting blood past the liver and (3) depressed hepato cellular function

**Clinical classification**

The syndrome may be classified into an acute type with or without an additional precipitating factor and a chronic type

*The acute type*

The acute type is best seen in fulminant virus hepatitis where the personality change is transient and coma supervenes rapidly The tremor may be short lived Fits mania and screaming attacks may be conspicuous especially in children In cirrhosis such spontaneous neuro psychiatric changes mark the later stages of the disease when liver cell failure is predominant

The various insults which precipitate the acute type in the cirrhotic patient do so either by impairing liver function or by increasing the amount of toxic nitrogenous substance in the intestine Gastro intestinal haemorrhage usually from oesophageal varices is by far the commonest precipitant The blood in the intestine is the equivalent of a large protein meal and the hypotension and anaemia impair the oxygen supply to the liver Other precipitants impairing liver function are acute infections acute alcoholism and drugs especially morphine and barbiturates Coma may also be precipitated in a patient with poor liver function by increasing nitrogen in the intestine by a large protein meal or by therapeutic doses of ammonium chloride methionine urea or choline

Paracentesis abdominis may also initiate coma although the mechanism is uncertain Electrolyte imbalance following the withdrawal of large quantities of sodium and water changing hepatic circulation when portal vein pressure is reduced and hypotension due to a vasovagal reaction may contribute

The carbonic anhydrase inhibitor acetazolamide (Diamox) given for some days occasionally causes neuro psychiatric changes in the patient with cirrhosis (Kunkel 1954) and there is an associated increase in blood ammonium levels (Webster and

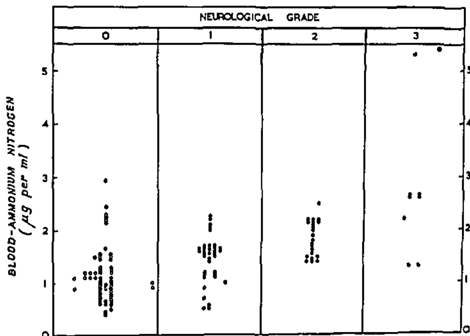



FIG 133 —Blood ammonium levels related to grade of neurological disability Solid circles neurological disability present or past open circles no neurological signs (*By courtesy of the Editor of the* Lancet)

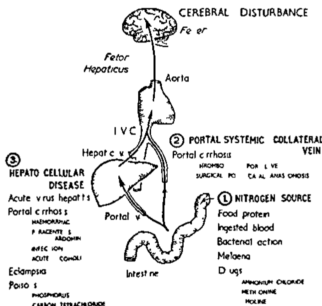



FIG 134 —The mechanism of neurological changes leading to hepatic coma The three important factors are (1) nitrogenous substances in the intestines (2) portal systemic collateral veins diverting blood past the liver and (3) depressed hepatocellular function (*By courtesy of the Editor of the* Brit med J)

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Fig 135 —The portal vein is occluded and all the contrast medium is diverted into collateral channels (*By courtesy of the Editor of the* Quart J Med)



Fig 136 —The portal vein is occluded and the contrast medium is diverted into a greatly dilated inferior mesenteric vein (*By courtesy of the Editor of the* Quart J Med)

Davidson 1956) Diamox impairs ammonium tolerance in liver disease and diminishes the uptake of ammonium by peripheral tissues (Dawson et al 1957)

*The chronic type*

The chronic type is associated with an extensive collateral circulation (Summerskill et al 1956) This may be demonstrated only by the technique of transplenic portal venography (Atkinson et al 1955) This circulation may follow thrombosis of the portal vein with diversion of the entire portal blood stream into collateral channels sometimes with distension of the inferior mesenteric vein to form a single collateral channel (Figs 135 and 136) Sometimes the umbilical vein is widely patent (Fig 137) There may be an extensive collateral circulation without a single major vessel (Fig 138) The construction of a surgical porta caval anastomosis for the relief of portal hypertension is followed by similar chronic neuro psychiatric symptoms in 10-15 per cent of patients (McDermott and Adams 1954 Riddell 1955)

The portal collateral circulation is so important in this group that it may be questioned whether it should be described under the heading of liver failure However there is always some liver disease in addition most frequently cirrhosis but sometimes only fatty change in the liver cells The intermittent neuro psychiatric disturbance may continue for as long as 6 years (Summerskill et al 1956)

**Treatment**

The intestines must be emptied and kept empty of all nitrogen-containing material All dietary protein is stopped and at least 1 600 calories are supplied daily as glucose drinks or as 20 per cent glucose through an intragastric drip When necessary 40 per cent dextrose is used intravenously through polythene tubing introduced via an ante cubital vein into the innominate vein or superior vena cava small veins would be thrombosed by glucose of this strength Care is taken to avoid fluid overload urinary volume is measured and lung bases and jugular vein filling examined regularly Potassium supplements are often needed when glucose is the only source of calories The exact amount is dictated by the history of the patient serum potassium values and electrocardiographic changes

During recovery protein is added in 20-gramme increments on alternate days The protein is divided between four meals Any relapse is treated by a return to the former regime Patients with an acute episode of coma soon achieve a normal dietary protein intake In the chronic group permanent protein restriction is needed to control mental symptoms (Summerskill et al 1956) the limit of tolerance is usually 40-50 grammes protein per day In this group an exacerbation of symptoms is treated by rest abstention from protein and a short course of chlortetracycline

Vitamins K and B complex supplements are given parenterally The lower intestine is emptied by an enema and this is repeated if necessary Oral magnesium sulphate 15 millilitres daily was also given for some patients in the chronic group and it was reported that they felt better when bowel actions were regular

Chlortetracycline given by mouth protects patients with liver disease from the adverse neurological effects of oral di methionine (Phear et al 1956) The bacterial flora of the small gut is increased in patients with hepatic cirrhosis and the number of organisms and their effect on methionine is much reduced by the antibiotic (Martini et al 1957) These results support the recommendation of wide spectrum antibiotic therapy by mouth Chlortetracycline is given if necessary by stomach tube a loading dose of 2 grammes being followed by 0 5 gramme 6-hourly for the duration of symptoms or to a maximum of one week Diarrhoea may complicate chlortetracycline



Fig 137 —A very large amount of contrast medium is diverted into a large umbilical vein which is filled from the left branch of the portal vein and passes towards the iliac veins Later radiographs showed filling of the inferior vena cava (*By courtesy of the Editor of the* Quart J Med )

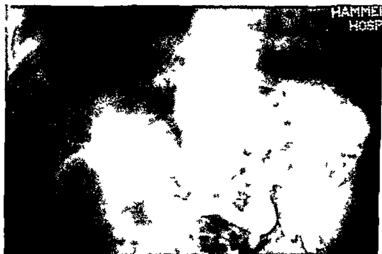



Fig 138 —The portal vein is patent There is an extensive collateral circulation mainly through the left gastric and oesophageal veins but also through some lumbar veins the left suprarenal vein and the inferior vena cava The intra hepatic radicles are distorted (*By courtesy of the Editor of the* Quart J Med )

therapy and necessitate withdrawal of the antibiotic Long term use is also associated with the emergence of resistant organisms Fisher and Faloon (1956) have reported the continued use of neomycin in the group with chronic neuro psychiatric changes Neomycin 6 grammes daily is the satisfactory antibiotic for routine use in the treatment of hepatic coma although it is most expensive

Precipitating factors are energetically treated Patients in impending coma are extremely sensitive to sedatives—all the symptoms and signs being exaggerated—and where possible these are avoided If the patient is uncontrollable half the usual dose of pentobarbital may be given morphine is absolutely contra indicated. Drugs known to induce hepatic coma such as ammonium salts ammonium exchange resins methionine urea chlorthiazide and Diamox are not to be administered

Gastro intestinal haemorrhage usually from oesophageal varices is a common precipitant of coma The bleeding may be a slow ooze and overt haematemesis or melaena delayed for some hours Gastric contents should therefore be examined and rectal examination performed in all patients where the precipitant of coma is uncertain Gastro intestinal haemorrhage with hepatic coma is always an indication for the Sengstaken oesophageal compression tube Blood transfusion is used to maintain the haemoglobin above 10 grammes per cent This may need to be prolonged and a piece of plastic tubing threaded into a large vein is often the surest way of delivering a constant supply of blood Toxic factors including significant and increasing amounts of ammonium develop rapidly in blood after shedding and where possible fresh blood is used for transfusion

Glutamic acid therapy is based on the supposition that ammonium toxicity is important in the genesis of hepatic coma Glutamic acid should react with the ammonium forming innocuous glutamine (Walshe 1953) Good results have been claimed in small series (Walshe 1953 Priest et al 1953) although this has not been confirmed by wider application under controlled conditions (Sherlock et al 1954 Alexander et al 1955) Although the blood ammonium level may fall after the administration of glutamic acid there is little clinical improvement (Sherlock et al 1956)

The evidence favouring the use of ACTH and cortisone in hepatic coma has not been convincing Evans et al (1953) found the drugs of no value and Ducci and Katz (1952) noted good results in some but failure in others Sborov et al (1955) noted definite but transitory benefit in 2 patients given ACTH Corticoid hormones are not recommended for hepatic coma occurring in patients with cirrhosis In patients where the syndrome complicates virus hepatitis recovery is so rare that very large doses of cortisone (1 000 milligrams daily) or preferably prednisolone (Metacortilan) may be tried if coma is deep

It is dangerous to give amino acids such as methionine which are toxic to these patients Amino acids cannot be metabolized by the failing liver and are already being excreted in the urine Similarly lipotropes such as choline prove of no value and may have toxic effects

## Results of treatment

In one series of 66 patients treated by the conservative regime 47 reached deep coma and 39 (58 per cent) recovered Of 34 patients in acute deep coma due to virus hepatitis or cirrhosis 11 survived (Table I Sherlock et al 1956) Results are even more impressive in the cirrhosis and hepatitis group if the pre comatose state is included for 24 of the 47 patients survived It is of course impossible to predict how many of these pre comatose patients would have passed into deep coma if untreated or how many would have recovered spontaneously Assessment of therapeutic results in hepatic coma is complicated by the unpredictable fluctuations in clinical course and the variable response to treatment of the numerous precipitating factors

## Prognosis

Prognosis (Table II) depends on the extent of liver cell failure The chronic group with relatively good liver function but with an extensive collateral circulation



FIG 137 —A very large amount of contrast medium is diverted into a large umbilical vein which is filled from the left branch of the portal vein and passes towards the iliac veins Later radiographs showed filling of the inferior vena cava (*By courtesy of the Editor of the* Quart J Med )




FIG 138 —The portal vein is patent There is an extensive collateral circulation mainly through the left gastric and oesophageal veins but also through some lumbar veins the left suprarenal vein and the inferior vena cava The intra hepatic radicles are distorted (*By courtesy of the Editor of the* Quart J Med )

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another complication or of coma recurring are considerable The majority of survivors however are alive one year later and treatment is eminently worthwhile This is particularly true of the acute hepatitis group in whom recovery is usually complete Altered liver function allowing the passage of toxic nitrogenous sub stances from the intestine to the brain is only one aspect of hepatic coma or indeed of liver failure The regime cannot control the electrolyte disturbance and other unrecognized metabolic changes which must be occurring when the liver fails Moreover no treatment directed solely towards correction of altered cerebral metabolism can be expected to succeed constantly in these circumstances The conservative regime seems the best available and will be modified when other effective remedies are discovered

## FETOR HEPATICUS

This is a sweetish slightly faecal smell of the breath and has been likened to that of aromatic amines mercaptans a freshly opened corpse or mice Fetor hepaticus occurs in patients with severe hepato cellular disease and also when there are extensive portal systemic venous collateral channels It occurs for instance after a surgical porta caval anastomosis It is presumably of intestinal origin for it becomes less intense or disappears after defaecation or when the gut flora has been changed by wide spectrum antibiotics The responsible substance is usually de toxicated by the liver but reaches the systemic circulation either by direct passage through a damaged liver or by the portal collaterals

Attempts have been made to isolate the substance responsible for the odour The most recent has been by Challenger and Walshe (1955) who found methyl mercaptan in the urine of a patient with hepatic coma who exhibited fetor hepaticus This substance can be exhaled in the breath It was speculated that it was derived from methionine the normal demethylating process being inhibited by liver damage

In patients with acute severe hepato cellular disease fetor hepaticus is a bad omen often preceding coma In patients with extensive portal collaterals it may occur transiently for long periods and may not be such a grave sign Fetor may be a useful diagnostic sign in patients seen for the first time in coma and in such cases it suggests that the coma is hepatic

## ASCITES

In the absence of a local cause and if associated with parenchymatous liver disease ascites implies hepato cellular failure The commonest cause is portal cirrhosis whether alcoholic nutritional following virus hepatitis or of unknown aetiology Ascites may complicate late or terminal biliary cirrhosis haemochromatosis hepatolenticular degeneration or bilharzial liver disease The association is how ever infrequent compared with portal cirrhosis

In the dog chronic hepatic venous congestion induced by constricting the inferior vena cava above the entry of the hepatic veins results in gross ascites the fluid having a high protein content The ascites associated with cardiac failure especially tricuspid incompetence constrictive pericarditis or with obstruction of the hepatic veins (Chiari s syndrome) presumably has a similar aetiology

TABLE I
RESULTS OF TREATMENT OF PATIENTS WITH HEPATIC COMA

| *Disease* | *Total* | *No reaching grade 3* | *Deaths* |
|---|---|---|---|
| Acute virus hepatitis | 13 | 8 | 6 |
| Cirrhosis (acute group) | 34 | 26 | 17 |
| Cirrhosis (chronic group) | 13 | 10 | 0 |
| Miscellaneous | 6 | 4 | 4 |
| Total | 66 | 48 | 27 |

TABLE II
FACTORS AFFECTING PROGNOSIS IN ACUTE HEPATIC COMA COMPLICATING HEPATIC CIRRHOSIS (SHERLOCK ET AL 1956)

| | | *Patients (all grades)* | *Patients reaching grade 3 coma* | *Deaths* |
|---|---|---|---|---|
| Total | | 34 | 26 | 17 |
| Age (years) | >50 | 26 | 20 | 15 |
| | <50 | 8 | 6 | 2 |
| Sex | M | 17 | 13 | 11 |
| | F | 17 | 13 | 6 |
| Ascites | + | 22 | 17 | 14 |
| | — | 12 | 9 | 3 |
| Serum bilirubin*† (mg per 100 ml ) | > 3 | 6 | 6 | 5 |
| | < 3 | 23 | 16 | 10 |
| Serum albumin (g per 100 ml ) | > 3 | 13 | 9 | 4 |
| | < 3 | 20 | 16 | 12 |
| Precipitating factor | + | 22 | 17 | 10 |
| | — | 12 | 9 | 7 |
| Grade when patient first seen | 1 | 13 | 5 | 5 |
| | 2 | 9 | 9 | 4 |
| | 3 | 12 | 12 | 8 |

Fo p t ents w th b l a y c rrhos s l d d
† O p t t d ed w th a few ho of dmi o a ds m b l ub n a d se m alb m l l w not mea d

combined with increased intestinal nitrogen have the best prognosis and the acute hepatitis group the worst In cirrhosis the outlook is poor if the patient has ascites jaundice and a low serum albumin level all indicative of poor liver cell function If treatment is begun early in the pre comatose state the chances of success are increased

The therapy of hepatic coma is only one facet of the whole management of the patient with chronic liver disease The chances of the patient developing

The part played by the antidiuretic hormone is probably very small for the antidiuretic hormone activity of urine in cirrhosis is normal (Stein et al 1954) and the cirrhotic liver can dispose of antidiuretic hormone normally (White et al 1951)

Oestrogens have a salt retaining action in animals (Thorn and Engel 1938) and are detoxicated by the liver (Pearlman 1948) Administration of oestradiol benzoate to patients with cirrhosis and ascites causes retention of sodium chloride and water (Preedy and Aitken 1956) and this may be yet another mechanism contributing to fluid retention in liver disease

## Clinical features

Ascites may appear suddenly or develop insidiously over the course of months with accompanying flatulent abdominal distension

The sudden onset of ascites may be the consequence of a gastro intestinal haemorrhage a respiratory tract infection or even an alcoholic debauch Any condition which lowers the plasma protein concentration may precipitate ascites A sudden increase in portal venous pressure due to thrombosis of the portal vein may cause transient ascites if the plasma protein concentration is also low

The insidious onset proclaims a worse prognosis possibly because it is not associated with any rectifiable factor There is gradually increasing abdominal distension and when the accumulation of fluid is sufficient to cause respiratory embarrassment dyspnoea occurs and this may be the reason for the patient seeking medical attention

## Treatment

The two most important factors in ascites formation are lowered serum albumin concentration and portal hypertension Raising plasma osmotic pressure—for instance by human albumin infusions—is of only transitory benefit It is not safe in the presence of ascites to lower the portal venous pressure by surgery There is however also an intense sodium retention presumably due to secondary stimulation of the adrenal cortex to produce aldosterone and the sodium content of body secretions such as urine faeces sweat and saliva is negligible Virtually all the sodium taken with food is retained with water to form ascites and on an unrestricted intake repeated paracenteses are necessary Each tap results in loss to the body of the protein contained in the ascitic fluid and as ascites re accumulates this is made up by protein manufactured with difficulty by the failing liver The patient shows progressive loss of flesh Re accumulation of ascites can be prevented by rigid restriction of dietary sodium The drain of protein into the ascites is stopped and the patient gains weight Plasma albumin rises until it reaches levels so high that ascites formation ceases At the onset one paracentesis is performed and the low sodium regime (22 milli equivalents equal 0 5 gramme of sodium per day) commenced in a hospital with *first class dietetic facilities After about* 2 months it can be continued at home These patients benefit from a high protein diet and this should only be reduced with the development of impending coma Most natural protein foods contain much salt Therefore to achieve a satisfactory intake salt poor protein supplements such as casilan must be used Mercurial diuretics are given twice weekly with ammonium chloride 3 grammes a day and potassium chloride 1 gramme a day It is most unusual for this small dose of ammonium chloride to precipitate hepatic coma

Ascites only complicates very severe attacks of virus hepatitis usually of longer than 3 weeks duration when the lesion is progressing to the subacute form There is always profound hypo albuminaemia

**Mechanism**

Patients with liver disease developing ascites retain sodium avidly (Eisenmenger et al 1950 Ricketts et al 1951) The mechanism of this must be extremely complex (Fig 139) It is partly related to the Starling hypothesis that the interchange of fluid between the blood and the tissue spaces is controlled by the balance of the capillary blood pressure forcing fluid into the tissue spaces and the difference

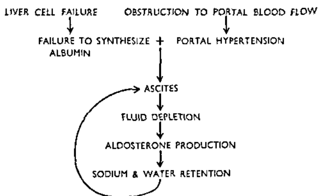



FIG 139—The mechanism of ascites production in cirrhosis of the liver (*By courtesy of the Editor of the* Practitioner)

between osmotic pressure in the vascular and extravascular compartments retaining fluid in the vascular compartment In cirrhosis the osmotic pressure of the plasma proteins falls due to the failure of the liver to manufacture albumin and the intrahepatic vascular distortion is associated with portal venous hypertension It is clear however that these are not the only mechanisms for increased amounts of the salt retaining hormones of the adrenal cortex (aldosterone) have been found in the urine of patients with cirrhosis forming ascites and this output can be stimulated by abdominal paracentesis when the need to retain sodium and water is accentuated (Axelrad et al 1955 Wolff et al 1956) The increased amounts of aldosterone might be due to hepatic functional impairment with failure to detoxicate the hormones Experiments on the perfused liver in animals (Miller and Axelrad 1954) and on surviving liver slices in man (Chart et al 1956) have shown that the liver metabolizes and inactivates the salt retaining hormone It could also be related to a continually acting compensatory mechanism directed towards the homeostasis of electrolyte and osmolarity conditions in the circulation in the face of pathological factors which cause a continuous loss of sodium and water into the extravascular space It seems likely that adrenal over production is combined with impaired hepatic inactivation Adrenalectomy has been used in the management of ascites Observations on dogs with experimental ascites induced by constriction of the thoracic vein show that bilateral adrenalectomy induces the sodium diuresis and disappearance of the ascites (Davis et al 1953) In man bilateral adrenalectomy has been performed in a patient with cirrhosis and intractable ascites Urinary sodium increased and the response to mercurial diuretics was improved although ascites persisted and dietary therapy with diuretics and exchange resins was still necessary (Marson 1954)

restriction combined with measures to deplete body sodium such as diuretics exchange resins and removal of oedema or ascitic fluid The syndrome is characterized by a lowering of urinary volume and chlorides a low serum sodium and chloride and rising blood urea levels with rapid gain in body weight and hypotension There is drowsiness weakness mental confusion nausea and muscular cramps Relief with diuresis and rise in blood pressure follows the administration of hypertonic saline solution intravenously Four patients with the hyponatraemia of liver failure were given saline therapy Given an unrestricted water intake the additional sodium was completely retained in isotonic dilution with further increase of an already expanded extracellular volume In 2 patients the hypertonic saline therapy was followed by pulmonary oedema and even seemed to accelerate death (Hecker and Sherlock 1956) Sodium should not be given to patients in liver failure unless there is clear evidence that sodium loss has been sustained for instance by vomiting diarrhoea or repeated abdominal paracenteses

The apparent hyponatraemia might be due to redistribution of sodium a relative greater fraction occurring in the extracellular compartment (Talso et al 1956) This concept has not been confirmed by actual measurements of sodium in the various body compartments The term dilution hyponatraemia should therefore be avoided since it is uncertain how much the low serum sodium is due to an expanded extracellular space (dilution) and how much to redistribution of sodium between extracellular and intracellular fluids A chronic state of hyponatraemia also occurs in chronic debilitating or wasting diseases such as advanced heart failure tuberculosis or cancer This could be effected either by retention of water or by excretion of sodium chloride Patients in terminal liver disease are certainly not excreting sodium and must therefore be retaining water This might be the result of the antidiuretic hormone the osmo receptors controlling its output being set at a lower level although there is little evidence that this is so Aldosterone must also be considered but this has little effect on water metabolism and excesses could not explain the phenomena seen in patients with terminal liver disease

The azotaemia seems unrelated to organic changes in the kidney It could be associated with the hypotension and renal circulatory failure and with the presence of blood in the intestine This however cannot be the whole explanation for blood urea may be raised before the development of either hypotension or gastro intestinal haemorrhage It is not clear whether the terminal rise in blood urea represents purely a circulatory deficiency or a more fundamental metabolic upset

Warm dry hands hypotension and a soft full pulse are common features of decompensated liver disease and the cardiac output is increased in patients with cirrhosis of the liver (Kowalski et al 1954) Peripheral venous blood is highly oxygenated (Silverstein 1956) The hyperdynamic circulation is not due solely to chronic anaemia for the hypotension precedes the terminal gastro intestinal haemorrhage and the patients are not severely anaemic The low blood pressure with increased cardiac output suggests vasodilatation but the mechanism of this is uncertain Shorr et al (1951) invoked a vasodilator material (V D M ) which is released in states of liver damage Although the significance of V D M is disputed it is clear that in liver failure there is a profound vasodilatation with a hyper dynamic circulation This increased blood flow is not to the brain for the level of consciousness correlates with the blood pressure neither does it seem to be to the kidney for the azotaemia must be in part circulatory In 1 patient the low

The state of nutrition improves and there is a rise in the serum albumin level When the serum albumin level has risen sufficiently the production of ascites will cease and at this stage it may be possible to relax sodium restriction Thus Eisenmenger (1952) found that after 10–40 months of sodium restriction 11 of 25 patients with cirrhosis and ascites could tolerate an unrestricted sodium intake

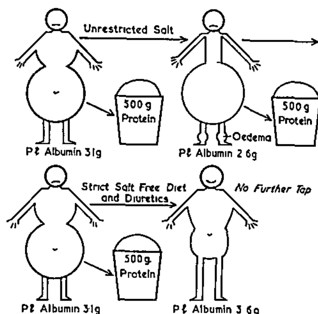



FIG 140 —Diagrams showing the effect of dietary salt restriction in the treatment of cirrhosis of the liver (*By courtesy of the Editor of the* Practitioner)

Davidson (1955) treated 30 patients with a low sodium regime and found a prompt diuresis in 4 a delayed diuresis 3–16 months later in 14 and failure usually due to continued alcoholism or gastro intestinal haemorrhage in 12 Dietary sodium restriction need not therefore be a permanent measure (Fig 140)

Therapeutic failures are usually due to the severity of the hepato cellular failure the patient entering the terminal stage of hyponatraemia (*see below*) to failure to co operate or to the presence of a complicating liver cell cancer

## TERMINAL ELECTROLYTE AND CIRCULATORY CHANGES

In the terminal stages of liver cell failure certain clinical and biochemical features are found which presage a fatal outcome Ascites if present fails to respond to the usual regime of dietary salt restriction and diuretics Urine output diminishes jaundice deepens the blood pressure falls and neuro psychiatric changes of impending hepatic coma are constant Biochemical changes include a falling serum sodium level low values are usual in the cirrhotic patients with ascites and oedema values below 130 milli equivalents per litre are ominous and recovery is most unusual when levels fall below 125 milli equivalents per litre There is a steady increase in the blood urea level

The mechanism of the hyponatraemia is very complex A comparison has been made with the low salt syndrome This condition is caused by excessive sodium

disease will not be affected if there is any component of biliary obstruction the consequent deficit of prothrombin and factor 7 will be corrected

If Christmas factor is believed lacking serum should be given Fresh blood transfusion is the only possible method of dealing with the profound bleeding diathesis of terminal liver failure Corticotrophin depresses fibrinolysin activity and may be useful if this abnormality is suspected (Kwaan et al 1956)

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oxygen saturation of hepatic venous blood suggested that the hepatic blood flow was reduced (Hecker and Sherlock 1956) It is known that the liver does not share in the increased cardiac output of other hyperdynamic states such as thyro toxicosis (Myers et al 1950) Indeed in the presence of hypotension liver blood flow is reduced and this may contribute to the liver failure resulting in hypotension with further worsening of liver function This is the rationale for raising systemic blood pressure Nor adrenaline is chosen because it is a peripheral constrictor with little effect either on the splanchnic circulation or cardiac output (Bearn et al 1951) This substance may have a dramatic temporary effect in improving the state of consciousness and increasing urinary volume and is always worth a trial Blood transfusion may be similarly effective

Diarrhoea may be a terminal feature in patients with liver failure but melaena or staphylococcal enteritis following the use of broad spectrum antibiotics must be excluded Diarrhoea can however occur apart from these two contingencies Its aetiology is obscure autopsy shows only a hyperaemic small intestine and colon and the bacteriology of the stools is not specific There is no treatment apart from attention to electrolyte balance

## BLOOD COAGULATION DEFECTS

The bleeding tendency of liver failure is of multiple causation The thrombo cytopenia associated with reticulo endothelial hyperplasia and splenomegaly is contributory but there is also a profound disturbance of many other factors concerned with haemostasis Many of these are proteins whose synthesis is presumably difficult when liver cell function fails Prothrombin migrates electro phoretically with the serum albumin fraction and is diminished in liver cell disease when serum albumin levels are low In contrast to the hypoprothrombinaemia of obstructive jaundice this deficiency is not corrected by parenteral vitamin K therapy Factor 5 is a globulin concerned with thromboplastin regeneration Deficiency may contribute to the bleeding tendency and prolonged one stage prothrombin time of patients with hepato cellular jaundice

Christmas factor is also concerned with thromboplastin regeneration and de ficiency may be found in patients with parenchymal liver disease (Cowling 1956) This defect is not revealed by either the one stage or the two stage prothrombin times

Fibrinogen is manufactured in the liver but deficiency is most unusual even in severe liver failure Recently however there has been renewed interest in increased fibrinolysin activity of blood in patients with cirrhosis of the liver (Kwaan et al 1956 Fearnley 1956) Kwaan and his colleagues thought that this increase did not correlate with the severity of the cirrhosis and it might be questioned whether this represents an actual failure of liver cell function

The two stage prothrombin time should be employed in all patients with liver cell failure The one stage method is not so useful being influenced only to a small extent by lack of prothrombin It may be within normal limits in the presence of prothrombin deficiency

Vitamin K parenterally should be given routinely to patients with liver failure It is innocuous and although the coagulation defect of parenchymatous liver

# CHAPTER 24

# INVESTIGATION OF PANCREATIC DYSFUNCTION

HENRY T HOWAT

## INTRODUCTION

PANCREATIC lesions often escape detection In acute pancreatitis a correct diagnosis is established before operation in less than half the cases and in cancer of the pancreas the early symptoms are rarely recognized until the spreading disease involves some contiguous structure such as the common bile duct This chapter is concerned with the application of physiological knowledge to the clinical study of pancreatic disease in man Disturbances of endocrine function will be considered only in so far as they are of value in diagnosing pancreatic disease affecting externally secreting tissue

### The clinical approach

No symptoms are pathognomonic of pancreatic disease Because of this the traditional and usual clinical approach to the problem of diagnosing pancreatic abnormalities is by a process of exclusion a method not without risk as Bright (1833) pointed out for this mode of reasoning presupposes an exact knowledge of the other organs which we may not possess The symptoms of pancreatic lesions mimic the clinical features of disease elsewhere in the upper abdomen and the frequent association of abnormalities in the pancreatic and biliary systems invalidates conclusions drawn solely from negative evidence

All authorities stress the need for a more positive approach The more constantly we bear the pancreas in mind as a possible seat of origin of obscure abdominal troubles the less likely we shall be to overlook its lesions (Garrod 1920) The clinical reviews of the past decade have made us increasingly familiar with the causes of pancreatic disease and with the development and course of pancreatic syndromes We rely on tests of pancreatic function to confirm a clinical suspicion that the pancreas is involved To determine the site of the lesion is but a first step in diagnosis we need also to determine the nature of the lesion Of the two problems the second is often the less difficult

Changes in both external and internal secretion of the pancreas may accompany pancreatic disease in most instances pancreatic function is depressed

Pancreatic dysfunction may be revealed by the following abnormalities

(1) Increased concentration of the pancreatic enzymes in body fluids

(2) Diminished secretory capacity of the pancreas Evidence of this is obtained (*a*) directly—by examining pancreatic juice obtained by intubating the duodenum and (*b*) *indirectly—by demonstrating impaired digestion and absorption of food*

(3) Abnormal carbohydrate tolerance

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to the upper abdomen are almost pathognomonic of acute pancreatitis Early and repeated estimations should be made so that a transient rise in level may not be overlooked A fall in serum amylase during the course of acute pancreatitis does not necessarily mean that improvement is taking place it may represent a destruction of functioning acinar tissue by the disease process It should not therefore be used as a prognostic test In more chronic pancreatic disease either inflammatory or neoplastic the serum amylase does not rise so dramatically Evidently here the functional activity of the gland diminishes *pari passu* with the progress of the disease The serum amylase however gives a comparatively constant value for the individual (Elman et al 1929) If the base line value for the individual is known a comparatively small elevation may prove significant and may be helpful in elucidating symptoms produced by disease in the upper abdomen

*Urinary amylase*

Urinary amylase has long been a popular test with British clinicians in acute pancreatitis Normally the kidney concentrates amylase present in serum In acute pancreatitis the concentration ratio persists and since the urinary amylase may remain higher a few hours longer than the serum amylase urinary values may be the test of choice at a later stage of the disease To minimize the effects of diuresis or dehydration on the concentration of amylase in the urine the result should be expressed in terms of output of amylase per hour or if time permits estimations should be made on 24 hour collections of urine In renal failure this test may give low values (Gray and Somogyi 1937 Huggins and Russell 1948) During the course of acute pancreatitis (even in the absence of shock) there may be transient renal impairment In these circumstances the fall in the serum amylase which usually occurs in 24–48 hours may be retarded and the rise in urinary amylase may be delayed (Danker and Heifetz 1951)

*Amylase in peritoneal fluid*

The peritoneal exudate of acute pancreatitis contains amylase Diagnostic paracentesis is a safe procedure which proves most helpful when a patient is first seen 3–4 days after the onset of illness by which time serum amylase values may be normal or equivocal (Zollinger et al 1954) A reddish brown fluid suggests haemorrhagic pancreatitis a turbid yellow fluid interstitial pancreatitis fat globules are present To exclude perforated peptic ulcer tests for hydrochloric acid and bile should be made As yet there is no means of differentiating the effusion accompanying intestinal obstruction Values exceeding 300 Somogyi units are said to support a diagnosis of acute pancreatitis (Keith et al 1950)

## Lipase

*Serum lipase*

In man there is probably little lipase of pancreatic origin normally present in serum though serum contains esterases capable of acting on the organic esters of fatty acids of low molecular weight In pancreatic disease however pancreatic lipase may enter the blood stream The distinction between serum lipase and serum esterase is not absolute Lipase hydrolyses the esters of higher fatty acids pre

## ESTIMATION OF PANCREATIC ENZYMES IN BODY FLUIDS

### Amylase

#### *Serum amylase*

The two main methods employed to measure serum amylase are the amyloclastic method of Wohlgemuth as modified by Somogyi and the saccharogenic method of Somogyi (1938) The first measures the initial stages of breakdown of starch to erythrodextrins the second is an estimation of the amount of reducing substance liberated in more complete starch digestion In practice the two methods show close parallelism *though the second is more precise (Somogyi 1932 1931–32)* Laboratories however should be familiar with both techniques for the saccharo genic method becomes more liable to error when there is hyperglycaemia and the amyloclastic technique may give fallacious results in the presence of jaundice Both states are not uncommon in pancreatic disease In some laboratories the normal range of 60–180 units given by Somogyi (1941) for the saccharogenic method has not been confirmed (One unit is defined as equivalent to 1 milligram of reducing substance expressed as glucose per 100 millilitres of serum ) In our experience values of 36–140 units are normal Comparison of values from different laboratories is difficult and workers using slight variations of technique may adopt a different range of normal values

Amylase is present in the blood serum of man in health Some of this may have its origin in the liver and salivary glands but the major portion arises from the pancreas An elevated value follows the passage of amylase into the blood stream from the acini or ductules of the pancreas and is found in pancreatitis and obstruction of the pancreatic duct The cause of the obstruction is not revealed by this functional test A raised serum amylase will only be found in pancreatic *disease so long as acinar cells are functioning*

Certain diseases apart from those of the pancreas itself may cause a rise in serum amylase for instance mumps and infective parotitis The diagnosis is as a rule clearly established in these cases by inspection Serum amylase values are said also to rise in renal failure with nitrogen retention (Danker and Heifetz *1951)* but Gross and Comfort (1956) have found normal values in this condition In a few cases of abdominal disease in which the pancreas was not primarily involved—perforated peptic ulcer small gut obstruction and peritonitis— raised serum amylase values have been recorded (Wapshaw 1949 1951 Musgrove 1950 Raffensperger 1950 1951 Edmondson et al 1952) In only rare instances has the value of amylase exceeded 500 units In some these occasional findings may be explained by the spasm of the sphincter of Oddi caused by opium derivatives used to relieve pain A rise in both serum amylase and lipase has been recorded in a small proportion of normal individuals who have been given mor phine and codeine (Gross et al 1951 Wapshaw 1953 Bogoch et al 1954 Nossel and Efron 1955) This effect of opiates is shared by pethidine (Gaensler et al 1948 Utendorfer and Bergh 1948) In practice care should be taken in interpreting serum enzyme values if opiates have been given in the preceding 24 hours (Bogoch et al 1954)

In pancreatic disease serum amylase estimations have proved of more value in the diagnosis of acute pancreatitis at an early stage of the disease than in chronic disease Values greater than 500 units in the presence of acute symptoms referred

present in the portal circulation It may be that this enzyme is carried over from the portal to the systemic veins through developing anastomotic channels for these findings are more common in patients who have subacute hepatitis and cirrhosis of the liver In rare instances also high serum values are found in advanced metastatic carcinoma of the liver when the primary tumour is in the colon (Johnson and Bockus 1940) or in the bronchus (Edmondson et al 1952)

*Lipase in urine*

Nothman et al (1955) claim to have demonstrated pancreatic lipase in the urine of normal man It is doubtful whether the method they use is sufficiently sensitive to justify this conclusion

## Trypsin

*Trypsin in serum*

It is not yet possible to determine directly that tryp in is present in the blood stream in pancreatic disease for blood serum in man contains powerful inhibitors of trypsin Nonetheless it has been supposed that at least some of the remote effects of acute pancreatitis are due to activated trypsinogen which is circulating in the peripheral blood Storer and Kazdan (1953) claim to have estimated trypsin in blood using the Anson and Mirsky method in which haemoglobin is the substrate

*Blood coagulation factors*

The addition of trypsin to blood *in vitro* alters the coagulation time When small amounts of trypsin were added Douglas and Colebrook (1916) showed that blood clotted more rapidly but with larger doses the coagulation time increased This is associated with increasing fibrinolytic activity (Shingleton et al 1953) Innerfield et al (1952) have investigated the changes in anti thrombin activity which occur after the injection of trypsin intravenously into dogs They have also described an increase in the anti thrombin titre in patients with acute pancreatitis in chronic relapsing pancreatitis during an exacerbation and in some patients with cancer of the pancreas A decreased titre was found in cystic fibro is and advanced cancer of the pancreas (Innerfield et al 1951) Doubts have been cast on the specificity of this test for abnormal titres both high and low have been found in appreciable numbers of patients who have no pancreatic disease (Griffith 1952 Dreiling et al 1954) Moreover the hypothesis that anti thrombin factors correspond with tryptic activity in the blood is not yet proved The role played by trypsin in coagulation *in vivo* is still not clear nor is it known how these anti thrombin factors are related to other proteolytic enzymes present in serum such as fibrinolysin and plasmin (Christensen and Macleod 1945)

*Trypsin in faeces*

To estimate the proteases in samples of stool does not provide an accurate assessment of pancreatic activity or function in adults

**Serum enzymes following stimulation of the external secretion**

The estimation of the serum enzymes in acute pancreatic disease is of such value that many workers in this field have modified the conditions of the tests to increase their value in cancer of the pancreas and in chronic and intermittent forms of pancreatitis This has been done in three ways (1) by stimulating the pancreas to secrete (2) by giving morphine which produces spasm of the sphincter of Oddi

ferentially whereas esterase acts on the esters of short chain fatty acids Since a considerable overlap exists *in the action of the two enzymes attempts have been* made with inhibitors and potentiators to increase the specificity of the tests for pancreatic lipase present in serum in pancreatic disease (Chiray et al 1931 Lagerlof 1945 1947)

In clinical practice the method used by most workers is a modification of the Loeren hart *technique for esterase described by Cherry and Crandall (1932) The substrate is* olive oil and in spite of the theoretical disadvantage of a reaction taking place in a two phase oil and water system it proves a satisfactory clinical test The replacement of olive oil by other substrates such as the simpler esters of fatty acids offers no advantage in clinical diagnosis In the Cherry and Crandall method the serum and olive oil are incubated for 24 hours which limits the value of the test in acute pancreatitis No other simple rapid and accurate method of estimating pancreatic lipase in serum, however has yet displaced this method in clinical laboratories In our experience the upper limit in normal subjects is 1 1 millilitres of N/20 sodium hydroxide per millilitre of serum

During the course of pancreatic disease serum lipase varies with serum amylase though they do not run wholly parallel (Fig 141) The estimation of serum amylase because it can be done more rapidly is the method of choice in acute pancreatitis

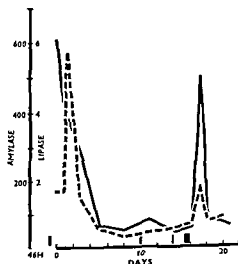



Fig 141 —Acute recurring pancreatitis Serum amylase and lipase values re corded at intervals during 4 episodes of upper abdominal distress Amylase—(continuous line) in units/100 ml Lipase —*(dotted line) in ml* N/20 Na OH/ml serum

though the serum lipase may be elevated in a higher proportion of cases (Comfort and Osterberg 1940) The elevation of serum lipase may be delayed a little and may be present longer than the rise in amylase (Johnson and Bockus 1940)

*As with amylase high* lipase values have been reported in a few instances of per forated ulcer intestinal obstruction and peritonitis not primarily due to acute pan creatitis and in a few normal individuals who have been given opium derivatives When the liver is damaged a raised serum lipase may sometimes be found even when there is no pancreatitis (Cummins and Bockus 1951) In these instances there seems to be little evidence that the abnormal liver produces additional esterase which splits fats or that the impaired liver cell cannot detoxify the small amounts of enzyme normally

was observed but in cases of pancreatitis in which high initial enzyme values had been observed and in cases examined within 10 weeks of an acute attack elevation occurred after secretin In pancreatitis and carcinoma of the pancreas with normal fasting values a rise in enzymes was sometimes seen Other workers have applied the principle of this provocative test to their enzyme methods—to the anti thrombin titre (Innerfield 1952) and to the paritol clotting test a test of increased blood coagulability (Shingleton et al 1952) Dreiling criticizes the theoretical basis of provocative tests in that the results depend on two variable and opposing factors—on the one hand duct obstruction and the extent of parenchymal damage on the other—and points out that in practice overlapping data and discordant

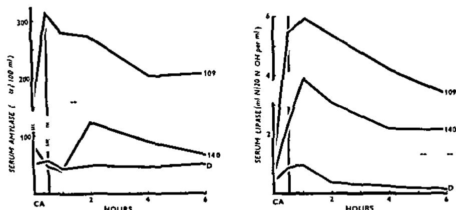



FIG 142 —The serum enzyme response evoked by secretin and pancreozymin in 3 patients with cancer of the pancreas (1) Patient 109—with normal glucose tolerance—the blood sugar was 109 milligrams per 100 millilitres 2½ hours after 50 grammes of glucose by mouth (2) Patient 140—with slightly impaired glucose tolerance—the blood sugar was 140 milligrams per 100 millilitres 2½ hours after 50 grammes of glucose by mouth (3) Patient D—with frank diabetes mellitus (*a*) Serum amylase values—the upper limit of normal after stimulation is 160 units (*b*) Serum lipase values—the upper limit of normal after stimulation is 1 3 millilitres

findings have been reported by different observers (Dreiling and Richman 1954 Dreiling and Janowitz 1956)

In a recent communication the Manchester workers have given an account of the results of estimating serum amylase and lipase after an intravenous injection of secretin followed by pancreozymin In normal subjects there was little change in serum enzyme values Significant increases of serum amylase and lipase were evoked in chronic relapsing pancreatitis and in cancer of the pancreas so long as sufficient acinar tissue remained active and capable of secreting In their hands an oral glucose tolerance test provided a means of assessing the extent of pancreatic damage in both the severer degrees of chronic pancreatitis and cancer of the pancreas When there was evidence in an impaired glucose tolerance test of extensive pancreatic damage elevated enzyme values were less often found after stimulation (Fig 142) These two tests were complementary and used together

thus increasing the obstruction in the duct system (Lagerlof 1945) and (3) by combining these two methods

The pancreatic stimulants used have been as a rule secretin and parasympatho mimetic drugs Popper and Necheles (1943) showed experimentally that secretin and mecholyl produced an elevation of serum lipase in dogs with a normal pancreas but not in animals in which the pancreas had atrophied Secretin alone produced no elevation in normal dogs but a rise was found after the pancreatic duct was tied (Popper et al 1943)

These observations suggested the two ways in which serum enzyme estimations following stimulation of the pancreas might be adapted for clinical use in man

**Serial determinations of serum enzymes after stimulation of the pancreas combined with morphine administration**

In this method a powerful stimulus is given to produce an adequate response from the gland at the same time morphine is given to contract the sphincter of Oddi temporarily When acinar function is normal a rise in serum enzymes would be expected but no elevation would occur in the presence of severe acinar destruc tion In practice this sharp distinction is not always observed in individual cases Myhre et al (1949) described their results when they combined secretin with mor phine A significant elevation of serum amylase or lipase was found in 70 per cent of normal subjects The morphine secretin test gave no rise in 9 patients with advanced pancreatic disease The percentage of positive tests is not sufficiently high to justify the use of this technique in clinical practice There seems little point in applying these tests to prove the destruction of pancreatic acinar tissue This is as a rule recognized clinically by stool examination or with much more certainty by examination of the duodenal contents after stimulation of the pancreas Burke et al (1950) moreover doubted the wisdom of combining the action of secretin with morphine because of the possible risk of aggravating latent pancreatitis

***Serial determination of serum enzymes following stimulation of the pancreas***

In this alternative method no morphine is given since the purpose of the test is different When the pancreas is normal no elevation in serum enzymes would be expected but in the presence of duct obstruction a rise would be obtained so long *as the pancreas is able to secrete enzyme Knight et al (1949) who did serial* determinations of serum amylase at intervals of 30 minutes following the injection of 1 milligram of prostigmine methyl sulphate intramuscularly have analysed the changes observed over 2 hours Normal cases showed no alteration In obstruction *of the duct and in destruction of the gland characteristic deviations* are obtained In most cases the response of the individual patient suffering from chronic pan creatitis is not decisive enough to be of diagnostic value It would appear that the dose of prostigmine used does not stimulate the external secretion of the pancreas sufficiently to achieve the aim of the test Moreover vagal stimulants such as prostigmine mecholyl and urecholine are not the best to use for this purpose since they may have both a direct action on the pancreas and a secondary action when the acid gastric juice produced passes into the duodenum

Lopusniak and Bockus (1950) in a study in which secretin only was adminis tered did serial estimations of serum amylase and lipase before and one 4 and 24 hours after giving the hormone In a control group no elevation of serum enzymes

minutes secretin is injected intravenously The duodenal and gastric contents are collected in 10-minute fractions for 60-80 minutes The volume of secretion of pancreatic juice following secretin given intravenously reaches its maximum in 10 minutes and then diminishes The dose used (1 clinical unit per kilogram of body weight) affects the secretion for some 60–80 minutes The mean volume of the duodenal contents secreted in 60 minutes in response to this dose of secretin was 202 5 millilitres in the series of 48 healthy adults reported by Lagerlof (1942) In man as in animals secretin stimulates the secretion of juice with high bicarbonate and low chloride concentration The maximum concentration of bicarbonate in duodenal contents usually reached in the second 10 minute interval is about 125 milli-equivalents per litre with a chloride concentration about 30 milli-equivalents per litre Concentration of bicarbonate thereafter diminishes as the volume diminishes and the concentration of chloride rises inversely The sum of the concentration of bicarbonate and chloride is about 155 milli equivalents per litre The mean total output of bicarbonate in 60 minutes was 19 38 milli-equivalents in Lagerlof s normal series The concentration of amylase trypsin and lipase drops to a low level in the second 10-minute period after which it rises as the rate of secretion of juice falls The total amounts of enzyme secreted per unit time are of the same magnitude in the different samples with the exception of the first 10-minute sample In the first 10 minute sample after secretin the concentration of the three enzymes rises in parallel fashion The total output is much increased and the parallelism exists in total output of all three enzymes following secretin At first Agren and Lagerlof claimed that secretin actively stimulated the secretion of enzymes but Lagerlof (1942) later concluded that this was not so The increased enzyme output in the first sample after secretin may be due to a washing out of pre formed enzymes from the duct system of the pancreas by secretin stimulated juice a phenomenon noted in animals Voegtlin et al (1934) considered that secretin stimulated a flow of enzymes It seems more likely that their secretin contained pancreozymin From the practical point of view the secretin test when repeated in the same individual gives repeatable results so far as volume and bicarbonate are concerned Greater variations occur in enzyme output

Lagerlof (1942) gave quantitative values for total volume bicarbonate output and output of enzymes in the duodenal contents following stimulation by secretin Diamond and Siegel (1940) considered that results expressed in terms of output per kilogram of body weight give a more accurate est mate of pancreatic function Confirmation of the results obtained in man by this secretin test have come from many sources Dreiling and Hollander (1950) and Dreiling (1951) who also gave 1 clinical unit of secretin per kilogram of body weight and continued the test for 80 minutes have given the following minimum normal values (1) for total volume—2 millilitres per kilogram (mean 3 2 $\pm$ 0 1 millilitre) (2) for maximum bicarbonate concentration—90 milli equivalents per litre (mean 108 $\pm$ 1 milli equivalent/L) (3) for amylase output—6 units per kilogram (mean 14 2 $\pm$ 0 4 units per kilogram)

*The secretin test in pancreatic disease*

In pancreatitis Lagerlöf (1939 1942) found two main types of abnormal response

*Type 1* —This is present during the first two weeks of the recovery phase after mild or moderately severe acute pancreatitis The enzyme secretion is depressed The characteristic finding is a reduction in the output of amylase while values for trypsin and lipase may be less affected—this state is reversible

*Type 2* —This is found when irreversible changes have taken place in the pancreas

were of value in estimating pancreatic involvement in chronic pancreatitis and carcinoma of the pancreas This secretin pancreozymin test was also positive in some patients with biliary tract disease occasionally after recovery from acute pancreatitis and rarely in cirrhosis of the liver (Howat et al 1955)

This method is of value because of the technical simplicity of the test The prerequisites of a successful provocative test are (1) an adequate stimulus which can be reproduced quantitatively is given to the pancreas in practice secretin or secretin and pancreozymin have proved the most useful (2) both amylase and lipase should be estimated in serum since we agree with Lopusniak and Bockus (1950) who consider that an increased serum lipase is a more sensitive index of pancreatic obstruction than a change in serum amylase (3) a concomitant glucose tolerance test is made

The evocative tests tend to give evidence of early pancreatic dysfunction and are probably the most sensitive index at present available in chronic relapsing pan creatitis and cancer of the pancreas Indeed evocative tests may be rather too sensitive because they may demonstrate functional change at the sphincter of Oddi when gall stones are present in the neck of the gall bladder or in the common bile duct This in itself however is not necessarily a disadvantage for the evocative test is here drawing attention to those patients who potentially at any rate are liable to develop pancreatitis and in whom a prophylactic operation on the biliary tract is most likely to lead to a cure

## DIRECT ESTIMATION OF PANCREATIC SECRETORY CAPACITY

### Examination of duodenal contents

In man pancreatic secretion cannot be obtained for analysis in a pure state but pancreatic function can be estimated directly by duodenal intubation This method is not entirely satisfactory for duodenal contents are an admixture of fluid derived from the intestine biliary tract and pancreas Early experiments with this technique were further complicated when food and food extracts were introduced into the duodenum to stimulate the pancreas In health fasting duo denal contents show wide variations Ågren and Lagerlof (1936) who possessed a purified preparation of secretin which could be given intravenously to stimulate the flow of pancreatic juice developed a method by which it could be used in man Their method is now generally followed with only minor variations

*The secretin test of pancreatic function*

In a fasting patient a radio opaque double lumen tube is passed and sited under the X ray screen so that one lumen drains the duodenum and the other the stomach A functional separation of stomach from duodenal contents is achieved at the pylorus by continuous aspiration of both tubes at a constant negative pressure of 25–40 milli metres of mercury Quantitative recovery of duodenal contents is aimed at the juice being collected into ice-cooled flasks containing glycerin to minimize inactivation of pancreatic enzyme Saliva is also aspirated from the mouth Preventing the passage of hydrochloric acid into the duodenum by continuous gastric aspiration obviates the the stimulant action of acid on the pancreas and the neutralization of the bicarbonate secreted by the pancreas The bile and intestinal juice present do not invalidate the test so long as all the duodenal juice is recovered After a control period of some 20–40

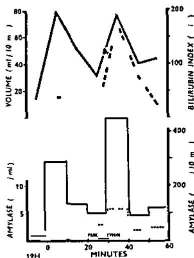



FIG 143—The secretin pancreozymin test in man Volume of duodenal contents bilirubin concentration concentration and total output of amylase in response to secretin (S) and pancreozymin (P)

*macrophages and crystals of cholesterol and calcium bilirubinate are present on* microscopy Culture of the duodenal contents is of doubtful value but is occasionally rewarding in patients with cholangitis

*Cancer cells*

Special techniques can be applied to the duodenal aspirate to search for exfoliated cancer cells (Lemon and Byrnes 1949 McNeer and Ewing 1949 Lemon 1952) In suspected cancer of the bile ducts and pancreas positive results are more frequently found before the patients develop jaundice and the growth has obstructed the ducts Rubin et al (1953) found cancer cells in 4 of the 8 cases of cancer of the pancreas they investigated by this method

## EVIDENCE OF IMPAIRED DIGESTION AND ABSORPTION OF FOOD

**Examination of the stools**

Indirect methods are also used to demonstrate insufficiency of the external secretion of the pancreas Qualitative changes in the naked eye and microscopic appearances of the faeces are less dependable characteristics than quantitative evidence which is obtained by correlating the faecal output with the dietary intake of fat and nitrogen yet inspection of the stools is a useful clinical observation In gross deficiency of external pancreatic secretion the stools are bulky and fat and recognizable macroscopically If in addition blood is present the stools may appear to have been smeared with silver or aluminium paint (Ogilvie 1955)

Microscopic examination of the stools from a patient on a mixed diet reveals highly refractile neutral fat globules which stain with Sudan III and undigested meat fibres are present In normal adults on a mixed diet the fat content of a single stool should not exceed 25 per cent of the dried weight of the stool (This criterion is only valid if no liquid paraffin is being taken by mouth )

as a result of necrosis fibrosis or duct obstruction A fall in both enzyme and bicarbonate output occurs

Transitional types of response are found

A reduced volume of the duodenal contents following stimulation by secretin is not such a characteristic feature of pancreatitis as is a lowered output of bicar bonate Lagerlof (1942) attributed this to the accompanying depression of gall bladder function frequently found in pancreatitis Hepatic bile flows more or less continuously into the duodenum to augment the volume of duodenal juice but bile does not raise the bicarbonate values to the same extent

*Cancer of the pancreas* —In cancer of the pancreas particularly of the head of the pancreas which is involving the common duct as well as the pancreatic duct a reduced volume of juice is accompanied by a fall in enzymes and bicarbonate

Dreiling (1953) has found in an extensive study with the secretin test two main abnormal responses in patients with pancreatic disease (1) a qualitative deficiency in which the volume of the secretin is sustained but the bicarbonate response and to a lesser extent the enzyme secretion is diminished This type is found in chronic inflammatory disease of the pancreas The characteristic defect is the depression of bicarbonate secretion and only in advanced cases are volume and enzyme secretion affected and (2) a quantitative deficiency in which there is a tendency to reduction in the volume with maintenance of bicarbonate and enzyme concentra tion *This is characteristic of pancreatic duct obstruction as seen in neoplasm* and is most marked in diffuse tumours and tumours involving the head of the pancreas which cause obstruction of a major duct To some extent a reduction in volume does occur however in tumours of the body of the pancreas also but this is not found in tumours of the tail of the pancreas

Secretin is not an enzyme stimulant Dreiling and Janowitz (1956) thought this accounted for the prominence of the bicarbonate defect in chronic pancreatitis Some workers who use the secretin test consider that enzyme estimations do not add information which cannot be got by measuring the volume and output of bicarbonate alone (Dornberger et al 1948) Others have tried to make the test more sensitive by combining a vagal stimulant such as mecholyl with secretin (Comfort and Osterberg 1941)

*The secretin pancreozymin test*

Pancreozymin a second hormonal substance separated by Harper and Raper (1943) *from secretin in mucosal extracts of small intestine* is a specific enzyme stimulant Trials with pancreozymin used in conjunction with secretin suggest that increased reliance can be placed on enzyme values secreted in response to this hormone (*see* Fig 143)

*Combined tests*

It is now our practice to combine this secretin pancreozymin test with the pro vocative test in which the serum enzymes are measured

**Further examination of duodenal contents**

*Microscopy and culture*

In suspected disease of the gall bladder and biliary tract advantage should be taken of the material obtained by duodenal intubation to note whether pus cells

of pancreatic insufficiency In practice this starch tolerance test is not sufficiently sensitive to give more information about pancreatic function than is available from the oral glucose tolerance test alone

## DEFICIENCY OF INTERNAL PANCREATIC SECRETION

Diffuse lesions of the pancreas may lead to impaired function of the islet cells Acute attacks of pancreatitis are accompanied by glycosuria and hyperglycaemia more frequently than is generally appreciated The disturbance of insulin production is sometimes mild and transient and may be overlooked unless a glucose tolerance test is made A permanent diabetes mellitus may result from a severe attack of acute pancreatitis but remarkable recovery can take place in the weeks and months which follow resolution of the inflammatory process Diabetes is more *likely to be present in recurring attacks of pancreatitis* and *is a feature of the* advanced stage of chronic pancreatitis As cancer of the pancreas progresses either from destruction of the gland by permeating tumour or from associated pancreatitis glucose tolerance tends to be progressively impaired When diabetes exists provocative tests are less likely to be of value in the diagnosis of pancreatic lesions

## OTHER TESTS

**Tests of gall bladder function**

The relationship of the gall bladder to pancreatic disease does not come within the scope of this chapter

**Liver function tests**

Liver function tests afford some help in studying pancreatic disease especially when the patient is jaundiced Repeated estimations of the amount of bilirubin present in serum are used to measure the severity and assess the progress of the jaundice *A progressive increase in serum bilirubin favours a neoplastic cause* for the jaundice Values of serum alkaline phosphatases exceeding 35 King Armstrong units per 100 millilitres of serum in the presence of normal flocculation tests (thymol turbidity and zinc turbidity tests) point to obstructive jaundice Even in the presence of jaundice due to cancer involving the head of the pancreas this critical level may not be reached A low prothrombin index which is rapidly restored to normal by the parenteral injection of vitamin K is characteristic of obstructive jaundice If the cause of the obstructive jaundice is cancer involving the bile ducts the amount of urobilinogen excreted in urine and faeces remains persistently low

In some patients cirrhosis of the liver may be found associated with chronic pancreatitis

**Serum electrolytes**

In pancreatic *necrosis disturbed electrolyte balance may be a feature of the* disease Changes occur in the electrocardiogram of a non specific type with inversion of T waves and depression of S T segments (Gottesman et al 1943) The Q T *interval may be prolonged and a U wave may appear*—features attributed

**Fat balance and nitrogen balance experiments**

Analysis of the faeces for total fat gives earlier information in the diagnosis of pancreatic disease than an analysis for total solids or faecal nitrogen (Dornberger et al 1948) These workers gave a 2 463 calorie diet which contained an average daily intake of 101 6 grammes of fat 117 6 grammes of protein (18 8 grammes of nitrogen) and 269 6 grammes of carbohydrate In normal persons the range of average daily loss of faecal nitrogen varied from 0 8 to 2 5 grammes (Wollaeger et al 1947) Fat balance studies with different dietary intakes have yielded comparable values (Cooke et al 1946 Black et al 1947) When a patient on a daily intake of 100 grammes of fat excretes more than 10 grammes of fat in the stools deficient fat absorption is present It has been claimed that if pancreatic deficiency is responsible for the excessive loss the pancreatic damage is roughly proportional to the output of fat in the stools (Dornberger et al 1948)

We use the method described by van de Kamer et al (1949) of estimating faecal fat Daily estimations of faecal fat are made and if the results indicate the presence of steatorrhoea the fat balance studies need only continue for a few days if however the results are equivocal the studies should continue for a period of 10 days to permit statistical evaluation of the data When steatorrhoea is demonstrated the stools may be further analysed for unsplit fat The extent of fat hydrolysis is not however a reliable index of pancreatic function The differentiation of pancreatic and malabsorptive steatorrhoea can usually be made on other criteria such as episodes of pain calcification or diabetes excessive loss of nitrogen in the stools or by more direct methods of proving pancreatic insufficiency such as the secretin test (Dornberger et al 1949) The fat balance technique can be used to assess the value of substitution therapy with pancreatin in the individual patient who has pancreatic steatorrhoea

*Other fats*

Fat linked with iodine (in Lipiodol) (Tremolieres 1940 Groen 1948 and Silverman and Shirkey 1955) or tagged with the isotope $^{131}$I have been used to study fat digestion and absorption (Shingleton et al 1955) Nardi (1954) used radioactive phosphate $^{32}$P as a measure of phospholipid synthesis in patients with pancreatic disease None of these methods has as yet displaced the conventional fat balance studies in clinical practice

*Protein*

In the study of cystic fibrosis of the pancreas in infants serial blood amino acid levels following a gelatin or casein meal have been used (West et al 1946 Anfanger and Heavenrich 1949) but Althausen and Uyeyama (1954) concluded these were an unreliable index in adult practice Chinn et al (1952) found high faecal radioactivity after pancreatectomy when patients were fed with casein labelled with the isotope $^{131}$I Shingleton et al (1955) gave a protein meal containing serum albumin tagged with $^{131}$I and made serial estimations of plasma radioactivity

*Starch*

Althausen and Uyeyama (1954) compared blood glucose levels following a test meal of 100 grammes of soluble starch and 100 grammes of glucose A smaller increase of blood sugar after starch than after glucose they consider characteristic

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to lowered potassium in the serum (Bockus and Raffensperger 1948) which should not be confused with the changes which occur in myocardial infarction A fall in serum calcium occurs from the third to the eleventh days in the severer grades of acute pancreatitis (Edmondson and Fields 1942 Edmondson and Berne 1944) This is due to the combination of calcium with fatty acid released in the upper abdomen by lipolysis Large amounts of calcium are present in this region at autopsy or if recovery takes place calcified areas in the region of the pancreas may be seen in a plain film of the upper abdomen A fall in serum calcium is less valuable as a diagnostic criterion than as a gauge of the severity of the process and may be used to assess prognosis (Edmondson et al 1952) It is not clear at the moment why calcium is not mobilized from body reserves to compensate for this fall in blood calcium

**Biopsy of the pancreas**

During inspection and palpation surgeons are frequently in doubt whether or not a tumour of the pancreas is malignant Biopsy of the pancreas is not without dangers and should be practised with caution and a recognition of the limited value of the method In most instances cancer of the pancreas is associated with some degree of pancreatitis either inflammatory or atrophic Reliance therefore can be put only on a positive finding of cancer in biopsies of the pancreas

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